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(54) Title: INHIBITORS OF HISTONE DEACETYLASE

(57) Abstract: The invention relates to the inhibition of histone deacetylase. The invention provides compounds and methods for inhibiting histone deacetylase enzymatic activity. The invention also provides compositions and methods for treating cell proliferative diseases and conditions.

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INHIBITORS OF HISTONE DEACETYLASE

[0001] This application claims priority from U.S. Provisional Patent Application No. 60/505884, filed on September 24, 2003, U.S. Provisional Patent Application No. 60/532973, filed on December 29, 2003, and U.S. Provisional Patent Application No. 60/561082, filed on April 9, 2004

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] This invention relates to the inhibition of histone deacetylase. More particularly, the invention relates to compounds and methods for inhibiting histone deacetylase enzymatic activity.

Summary of the Related Art

[0003] In eukaryotic cells, nuclear DNA associates with histones to form a compact complex called chromatin. The histones constitute a family of basic proteins which are generally highly conserved across eukaryotic species. The core histones, termed H2A, H2B, H3, and H4, associate to form a protein core. DNA winds around this protein core, with the basic amino acids of the histones interacting with the negatively charged phosphate groups of the DNA. Approximately 146 base pairs of DNA wrap around a histone core to make up a nucleosome particle, the repeating structural motif of chromatin.

[0004] Csordas, *Biochem. J.*, **286**: 23-38 (1990) teaches that histones are subject to posttranslational acetylation of the α,ε-amino groups of *N*-terminal lysine residues, a reaction that is catalyzed by histone acetyl transferase (HAT1). Acetylation neutralizes the positive charge of the lysine side chain, and is thought to impact chromatin structure. Indeed, Taunton *et al.*, *Science*, **272**: 408-411 (1996), teaches that access of transcription factors to chromatin templates is enhanced by histone hyperacetylation. Taunton *et al.* further teaches that an enrichment in underacetylated histone H4 has been found in transcriptionally silent regions of the genome.

[0005] Histone acetylation is a reversible modification, with deacetylation being catalyzed by a family of enzymes termed histone deacetylases (HDACs). Grozinger *et al.*, *Proc. Natl. Acad. Sci. USA*, **96**: 4868-4873 (1999), teaches that HDACs are divided into two classes, the first represented by yeast Rpd3-like proteins, and the second represented by yeast Hda1-like proteins. Grozinger *et al.* also teaches that the human HDAC1, HDAC2, and HDAC3 proteins are members of the first class of HDACs, and discloses new proteins, named HDAC4, HDAC5, and HDAC6, which are members of the second class of HDACs. Kao *et al.*, *Genes & Dev.*, **14**: 55-66 (2000), discloses HDAC7, a new member of the second class of HDACs. More recently, Hu *et al.* J. Bio. Chem. **275**:15254-13264 (2000) and Van den Wyngaert, *FEBS*, **478**: 77-83 (2000) disclose HDAC8, a new member of the first class of HDACs.

[0006] Richon *et al.*, *Proc. Natl. Acad. Sci. USA*, **95**: 3003-3007 (1998), discloses that HDAC activity is inhibited by trichostatin A (TSA), a natural product isolated from *Streptomyces hygroscopicus*, and by a synthetic compound, suberoylanilide hydroxamic acid (SAHA). Yoshida and Beppu, *Exper. Cell Res.*, **177**: 122-131 (1988), teaches that TSA causes arrest of rat fibroblasts at the G_1 and G_2 phases of the cell cycle, implicating HDAC in cell cycle regulation. Indeed, Finnin *et al.*, *Nature*, **401**: 188-193 (1999), teaches that TSA and SAHA inhibit cell growth, induce terminal differentiation, and prevent the formation of tumors in mice. Suzuki *et al.*, U.S. Pat. No. 6,174,905, EP 0847992, JP 258863/96, and Japanese Application No. 10138957, disclose benzamide derivatives that induce cell differentiation and inhibit HDAC. Delorme *et al.*, WO 01/38322 and PCT/IB01/00683, disclose additional compounds that serve as HDAC inhibitors.

[0007] The molecular cloning of gene sequences encoding proteins with HDAC activity has established the existence of a set of discrete HDAC enzyme isoforms. Some isoforms have been shown to possess specific functions, for example, it has been shown that HDAC-6 is involved in modulation of microtubule activity. However, the role of the other individual HDAC enzymes has remained unclear.

[0008] These findings suggest that inhibition of HDAC activity represents a novel approach for intervening in cell cycle regulation and that HDAC inhibitors have great therapeutic potential in the treatment of cell proliferative diseases or conditions. To date, few inhibitors of histone deacetylase are known in the art.

BRIEF SUMMARY OF THE INVENTION

[0009] Ortho-amino benzamides are known HDAC inhibitors. Substitutions at the ortho- and meta-positions relative to the amino group are detrimental to the potency of the inhibitors; however, some small substituents such as $-CH_3$, -F, or $-OCH_3$ can be tolerated to a certain extent. We have now found that *o*-amino benzamide HDAC inhibitors having a much bigger but flat aromatic and heteroaromatic substituents such as phenyl, furyl, thienyl and the like para to the amino moiety are not only well tolerated but cause significant increase in HDAC inhibition activity.

[0010] Accordingly, the present invention provides new compounds and methods for treating cell proliferative diseases. The invention provides new inhibitors of histone deacetylase enzymatic activity.

[0011] In a first aspect, the invention provides compounds that are useful as inhibitors of histone deacetylase.

[0012] In a second aspect, the invention provides a composition comprising an inhibitor of histone deacetylase according to the invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, excipient, or diluent.

[0013] In a third aspect, the invention provides a method of inhibiting histone deacetylase in a cell, comprising contacting a cell in which inhibition of histone deacetylase is desired with an inhibitor of histone deacetylase of the invention.

[0014] The foregoing merely summarizes certain aspects of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below. All publications (patent or other) are hereby incorporated by reference in their entirety; in the event of any conflict between these materials and the present specification, the present specification shall control.

BRIEF DESCRIPTION OF THE DRAWING

[0015] The figures displays antineoplastic effects of a histone deacetylase inhibitor according to the invention on human tumor xenografts *in vivo*, as described in Assay Example 2, *infra*.

[0016] Fig. 1 displays antineoplastic effects of a histone deacetylase inhibitor in hct116 human colorectal carcinoma cells using compound 6.

[0017] Fig. 2 displays antineoplastic effects of a histone deacetylase inhibitor in A549 human lung cancer using compound 29.

[0018] Fig. 3 displays antineoplastic effects of a histone deacetylase inhibitor in SW48 human colorectal cancer using compound 29.

[0019] Fig. 4 displays antineoplastic effects of a histone deacetylase inhibitor in W48 human colorectal cancer usingcompound 67.

[0020] Fig. 5 displays antineoplastic effects of a histone deacetylase inhibitor in A549 human lung cancer using compound 258aa.

[0021] Fig. 6 displays antineoplastic effects of a histone deacetylase inhibitor in A549 human lung cancer using compound 43.

[0022] Fig. 7 displays antineoplastic effects of a histone deacetylase inhibitor in A431 vulval carcinoma using compound 43.

[0023] Fig. 8 displays antineoplastic effects of a histone deacetylase inhibitor in A431 vulval carcinoma using compound 258aa.

[0024] Fig. 9 displays antineoplastic effects of a histone deacetylase inhibitor in hct116 human colorectal cancer using compound 258aa.

[0025] Fig. 10 displays antineoplastic effects of a histone deacetylase inhibitor in colo205 human colorectal cancer using compound 29.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0026] The invention provides compounds and methods for inhibiting histone deacetylase enzymatic activity. The invention also provides compositions and methods for treating cell

proliferative diseases and conditions. The patent and scientific literature referred to herein establishes knowledge that is available to those with skill in the art. The issued patents, applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of inconsistencies, the present disclosure will prevail.

[0027] For purposes of the present invention, the following definitions will be used (unless expressly stated otherwise):

[0028] As used herein, the terms "histone deacetylase" and "HDAC" are intended to refer to any one of a family of enzymes that remove acetyl groups from the ω-amino groups of lysine residues at the *N*-terminus of a histone. Unless otherwise indicated by context, the term "histone" is meant to refer to any histone protein, including H1, H2A, H2B, H3, H4, and H5, from any species. Preferred histone deacetylases include class I and class II enzymes. Preferably the histone deacetylase is a human HDAC, including, but not limited to, HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, HDAC-8, HDAC-9, HDAC-10, and HDAC-11. In some other preferred embodiments, the histone deacetylase is derived from a protozoal or fungal source.

[0029] The terms "histone deacetylase inhibitor" and "inhibitor of histone deacetylase" are used to identify a compound having a structure as defined herein, which is capable of interacting with a histone deacetylase and inhibiting its enzymatic activity. "Inhibiting histone deacetylase enzymatic activity" means reducing the ability of a histone deacetylase to remove an acetyl group from a histone. In some preferred embodiments, such reduction of histone deacetylase activity is at least about 50%, more preferably at least about 75%, and still more preferably at least about 90%. In other preferred embodiments, histone deacetylase activity is reduced by at least 95% and more preferably by at least 99%.

[0030] Preferably, such inhibition is specific, *i.e.*, the histone deacetylase inhibitor reduces the ability of a histone deacetylase to remove an acetyl group from a histone at a concentration that is lower than the concentration of the inhibitor that is required to produce another, unrelated biological effect. Preferably, the concentration of the inhibitor required for histone deacetylase inhibitory activity is at least 2-fold lower, more preferably at least 5-fold lower, even more preferably at least 10-fold lower, and most preferably at least 20-fold lower than the concentration required to produce an unrelated biological effect.

[0031] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (*e.g.*, alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an "alkyl" moiety generally refers to a monovalent radical (*e.g.*

CH_3-CH_2-), in certain circumstances a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (*e.g.*, -CH_2-CH_2-), which is equivalent to the term "alkylene." (Similarly, in circumstances in which a divalent moiety is required and is stated as being "aryl," those skilled in the art will understand that the term "aryl" refers to the corresponding divalent moiety, arylene.) All atoms are understood to have their normal number of valences for bond formation (*i.e.*, 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). On occasion a moiety may be defined, for example, as $(A)_a$-B-, wherein a is 0 or 1. In such instances, when a is 0 the moiety is B- and when a is 1 the moiety is A-B-.

[0032] For simplicity, reference to a "C_n-C_m" heterocyclyl or "C_n-C_m" heteroaryl means a heterocyclyl or heteroaryl having from "n" to "m" annular atoms, where "n" and "m" are integers. Thus, for example, a C_5-C_6-heterocyclyl is a 5- or 6- membered ring having at least one heteroatom, and includes pyrrolidinyl (C_5) and piperidinyl (C_6); C_6-hetoaryl includes, for example, pyridyl and pyrimidyl.

[0033] The term "hydrocarbyl" refers to a straight, branched, or cyclic alkyl, alkenyl, or alkynyl, each as defined herein. A "C_0" hydrocarbyl is used to refer to a covalent bond. Thus, "C_0-C_3-hydrocarbyl" includes a covalent bond, methyl, ethyl, ethenyl, ethynyl, propyl, propenyl, propynyl, and cyclopropyl.

[0034] The term "alkyl" as employed herein refers to straight and branched chain aliphatic groups having from 1 to 12 carbon atoms, preferably 1-8 carbon atoms, and more preferably 1-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl. A "C_0" alkyl (as in "C_0-C_3-alkyl") is a covalent bond (like "C_0" hydrocarbyl).

[0035] The term "alkenyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon double bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkenyl groups include, without limitation, ethenyl, propenyl, butenyl, pentenyl, and hexenyl.

[0036] The term "alkynyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon triple bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkynyl groups include, without limitation, ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[0037] An "alkylene," "alkenylene," or "alkynylene" group is an alkyl, alkenyl, or alkynyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups.

Preferred alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene. Preferred alkenylene groups include, without limitation, ethenylene, propenylene, and butenylene. Preferred alkynylene groups include, without limitation, ethynylene, propynylene, and butynylene.

[0038] The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbons, wherein the cycloalkyl group additionally is optionally substituted. Preferred cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[0039] The term "heteroalkyl" refers to an alkyl group, as defined hereinabove, wherein one or more carbon atoms in the chain are replaced by a heteroatom selected from the group consisting of O, S, and N.

[0040] An "aryl" group is a C_6-C_{14} aromatic moiety comprising one to three aromatic rings, which is optionally substituted. Preferably, the aryl group is a C_6-C_{10} aryl group. Preferred aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl. An "aralkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted. Preferably, the aralkyl group is (C_1-C_6)alk(C_6-C_{10})aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

[0041] A "heterocyclic" group (or "heterocyclyl) is an optionally substituted non-aromatic mono-, bi-, or tricyclic structure having from about 3 to about 14 atoms, wherein one or more atoms are selected from the group consisting of N, O, and S. One ring of a bicyclic heterocycle or two rings of a tricyclic heterocycle may be aromatic, as in indan and 9,10-dihydro anthracene. The heterocyclic group is optionally substituted on carbon with oxo or with one of the substituents listed above. The heterocyclic group may also independently be substituted on nitrogen with alkyl, aryl, aralkyl, alkylcarbonyl, alkylsulfonyl, arylcarbonyl, arylsulfonyl, alkoxycarbonyl, aralkoxycarbonyl, or on sulfur with oxo or lower alkyl. Preferred heterocyclic groups include, without limitation, epoxy, aziridinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, thiazolidinyl, oxazolidinyl, oxazolidinonyl, and morpholino. In certain preferred embodiments, the heterocyclic group is fused to an aryl, heteroaryl, or cycloalkyl group. Examples of such fused heterocycles include, without limitation, tetrahydroquinoline and dihydrobenzofuran. Specifically excluded from the scope of this term are compounds where an annular O or S atom is adjacent to another O or S atom.

[0042] In certain preferred embodiments, the heterocyclic group is a heteroaryl group. As used herein, the term "heteroaryl" refers to optionally substituted groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 pi electrons shared in a cyclic array; and having, in addition to carbon atoms, between one or more heteroatoms selected from the group

consisting of N, O, and S. For example, a heteroaryl group may be pyrimidinyl, pyridinyl, benzimidazolyl, thienyl, benzothiazolyl, benzofuranyl and indolinyl. Preferred heteroaryl groups include, without limitation, thienyl, benzothienyl, furyl, benzofuryl, dibenzofuryl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indolyl, quinolyl, isoquinolyl, quinoxalinyl, tetrazolyl, oxazolyl, thiazolyl, and isoxazolyl.

[0043] A "heteroaralkyl" or "heteroarylalkyl" group comprises a heteroaryl group covalently linked to an alkyl group, either of which is independently optionally substituted or unsubstituted. Preferred heteroalkyl groups comprise a C_1-C_6 alkyl group and a heteroaryl group having 5, 6, 9, or 10 ring atoms. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms. Examples of preferred heteroaralkyl groups include pyridylmethyl, pyridylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, thiazolylmethyl, and thiazolylethyl.

[0044] An "arylene," "heteroarylene," or "heterocyclylene" group is an aryl, heteroaryl, or heterocyclyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups.

[0045] Preferred heterocyclyls and heteroaryls include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0046] As employed herein, when a moiety (*e.g.*, cycloalkyl, hydrocarbyl, aryl, heteroaryl, heterocyclic, urea, etc.) is described as "optionally substituted" it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non-hydrogen

substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo (*e.g.*, an annular -CH- substituted with oxo is -C(O)-) nitro, halohydrocarbyl, hydrocarbyl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, acyl, carboxy, hydroxyalkyl, alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups. Preferred substituents, which are themselves not further substituted (unless expressly stated otherwise) are:

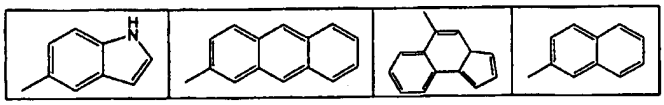
(a) halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino, guanidino,

(b) C_1-C_5 alkyl or alkenyl or arylalkyl imino, carbamoyl, azido, carboxamido, mercapto, hydroxy, hydroxyalkyl, alkylaryl, arylalkyl, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkoxy, C_1-C_8 alkoxycarbonyl, aryloxycarbonyl, C_2-C_8 acyl, C_2-C_8 acylamino, C_1-C_8 alkylthio, arylalkylthio, arylthio, C_1-C_8 alkylsulfinyl, arylalkylsulfinyl, arylsulfinyl, C_1-C_8 alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C_0-C_6 *N*-alkyl carbamoyl, C_2-C_{15} *N*,*N*-dialkylcarbamoyl, C_3-C_7 cycloalkyl, aroyl, aryloxy, arylalkyl ether, aryl, aryl fused to a cycloalkyl or heterocycle or another aryl ring, C_3-C_7 heterocycle, C_5-C_{15} heteroaryl or any of these rings fused or spiro-fused to a cycloalkyl, heterocyclyl, or aryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; and

(c) $-(CH_2)_s-NR^{30}R^{31}$, wherein s is from 0 (in which case the nitrogen is directly bonded to the moiety that is substituted) to 6, and R^{30} and R^{31} are each independently hydrogen, cyano, oxo, carboxamido, amidino, C_1-C_8 hydroxyalkyl, C_1-C_3 alkylaryl, aryl-C_1-C_3 alkyl, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkoxy, C_1-C_8 alkoxycarbonyl, aryloxycarbonyl, aryl-C_1-C_3 alkoxycarbonyl, C_2-C_8 acyl, C_1-C_8 alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, aroyl, aryl, cycloalkyl, heterocyclyl, or heteroaryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; or

R^{30} and R^{31} taken together with the N to which they are attached form a heterocyclyl or heteroaryl, each of which is optionally substituted with from 1 to 3 substituents from (a), above.

[0047] In addition, substituents on cyclic moieties (i.e., cycloalkyl, heterocyclyl, aryl, heteroaryl) include 5-6 membered mono- and 9-14 membered bi-cyclic moieties fused to the parent cyclic moiety to form a bi- or tri-cyclic fused ring system. For example, an optionally substituted phenyl includes, but not limited to, the following:



[0048] A "halohydrocarbyl" is a hydrocarbyl moiety in which from one to all hydrogens have been replaced with one or more halo.

[0049] The term "halogen" or "halo" as employed herein refers to chlorine, bromine, fluorine, or iodine. As herein employed, the term "acyl" refers to an alkylcarbonyl or arylcarbonyl substituent. The term "acylamino" refers to an amide group attached at the nitrogen atom (*i.e.*, R-CO-NH-). The term "carbamoyl" refers to an amide group attached at the carbonyl carbon atom (*i.e.*, NH_2-CO-). The nitrogen atom of an acylamino or carbamoyl substituent is additionally substituted. The term "sulfonamido" refers to a sulfonamide substituent attached by either the sulfur or the nitrogen atom. The term "amino" is meant to include NH_2, alkylamino, arylamino, and cyclic amino groups. The term "ureido" as employed herein refers to a substituted or unsubstituted urea moiety.

[0050] The term "radical" as used herein means a chemical moiety comprising one or more unpaired electrons.

[0051] A moiety that is substituted is one in which one or more hydrogens have been independently replaced with another chemical substituent. As a non-limiting example, substituted phenyls include 2-flurophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2-fluoro-3-propylphenyl. As another non-limiting example, substituted *N*-octyls include 2,4 dimethyl-5-ethyl-octyl and 3-cyclopentyl-octyl. Included within this definition are methylenes (-CH_2-) substituted with oxygen to form carbonyl -CO-).

[0052] An "unsubstituted" moiety as defined above (*e.g.*, unsubstituted cycloalkyl, unsubstituted heteroaryl, etc.) means that moiety as defined above that does not have any of the optional substituents for which the definition of the moiety (above) otherwise provides. Thus, for example, while an "aryl" includes phenyl and phenyl substituted with a halo, "unsubstituted aryl" does not include phenyl substituted with a halo.

[0053] Throughout the specification preferred embodiments of one or more chemical substituents are identified. Also preferred are combinations of preferred embodiments. For example, paragraph [0066] describes preferred embodiments of Cy^2 in the compound of formula (1) and paragraph [0082] describes preferred embodiments of R^2 to R^4 of the compound of formula (1). Thus, also contemplated as within the scope of the invention are compounds of formula (1) in which Cy^2 is as described in paragraph [0066] and Ay^2 and R^1 to R^4 are as described in paragraph [0082].

[0054] Some compounds of the invention may have chiral centers and/or geometric isomeric centers (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers. The invention also comprises all tautomeric forms of the compounds disclosed herein.

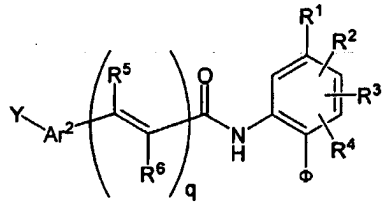
[0055] The compounds of the invention may be administered in the form of an *in vivo* hydrolyzable ester or *in vivo* hydrolyzable amide. An *in vivo* hydrolyzable ester of a compound of the invention containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester

which is hydrolyzed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}-alkoxymethyl esters (*e.g.*, methoxymethyl), C_{1-6}-alkanoyloxymethyl esters (*e.g.*, for example pivaloyloxymethyl), phthalidyl esters, C_{3-8}-cycloalkoxycarbonyloxyC_{1-6}-alkyl esters (*e.g.*, 1-cyclohexylcarbonyloxyethyl); 1,3-dioxolen-2-onylmethyl esters (*e.g.*, 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}-alkoxycarbonyloxyethyl esters (*e.g.*, 1-methoxycarbonyloxyethyl) and may be formed at any carboxy group in the compounds of this invention.

[0056] An *in vivo* hydrolyzable ester of a compound of the invention containing a hydroxy group includes inorganic esters such as phosphate esters and a-acyloxyalkyl ethers and related compounds which as a result of the in vivo hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in vivo hydrolyzable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(*N*,*N*-dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), *N*,*N*-dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring. A suitable value for an *in vivo* hydrolyzable amide of a compound of the invention containing a carboxy group is, for example, a *N*-C_{1-6}-alkyl or N,N-di-C_{1-6}-alkyl amide such as *N*-methyl, *N*-ethyl, *N*-propyl, *N*,*N*-dimethyl, *N*-ethyl-*N*-methyl or *N*,*N*-diethyl amide.

Compounds

[0057] In the first aspect, the invention comprises the histone deacetylase inhibitors of formula (1):



(1)

or a pharmaceutically acceptable salt thereof, wherein

Ar^2 is a saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl, optionally containing one, two, three, or four annular heteroatoms per ring optionally substituted with one or more groups selected from C_1-C_7-alkyl, hydroxy, C_1-C_7-alkoxy, halo, and amino, provided that an annular O or S is not adjacent to another annular O or S;

R^5 and R^6 are independently selected from the group consisting of hydrogen, C_1-C_7-alkyl, aryl, and aralkyl;

R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen, halogen, $-NH_2$, nitro, hydroxy, aryl, heterocyclyl, C_3-C_8-cycloalkyl, heteroaryl, C_1-C_7-akyl, haloalkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, C_1-C_7-acyl, C_1-C_7-alkyl-aryloxy, C_1-C_7-alkyl-arylsulfanyl, C_1-C_7-alkyl-arylsulfinyl, C_1-C_7-alkyl-arylsulfonyl, C_1-C_7-alkyl-arylaminosulfonyl, C_1-C_7-alkyl-arylamine, C_1-C_7-alkynyl-C(O)-amine, C_1-C_7-alkenyl-C(O)-amine, C_1-C_7-alkynyl-R^9, C_1-C_7-alkenyl-R^9 wherein R^9 is hydrogen , hydroxy, amino, C_1-C_7-alkyl or C_1-C_7-alkoxy;

q is 0 or 1;

R^1 is a mono-, bi-, or tri-cyclic aryl or heteroaryl, each of which is optionally substituted;

Φ is $-NH_2$ or -OH and

Y is any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms;

provided that

when R^1 is *N*-imidazolyl, R^2-R^4 are H, q is 0, and Ar^2 is pyridine, Y is not Cl; and

when R^1 is *p*-aminophenyl, R^2-R^4 are H, q is 0, and Ar^2 is phenyl, Y is not H.

[0058] The atoms that comprise the Y moiety are preferably those found in pharmaceuticals, including, but not limited to, H, C, N, O, S, F, Cl, Br, I, and P. Numerous representative examples of Y are displayed in paragraphs [0061] - [0095], [0105] – [0106], and [0111] - [0148]. Y moieties of the compounds of the present invention also can be found in the following publications (either *per se* or as part of a disclosed molecule): WO 03/087057, WO 03/076422, WO 03/024448, US 6,174,905, JP 11-269146 (1999), JP 11-302173 (1999), JP 2001131130, EP 0847992, JP 10152462, JP 2002332267, JP 11302173, and JP 2003137866. For example, in these publications many different Y moieties are readily identified in molecules of structure Y-Ar^2-$(CH=CH)_a$-C(O)-NH-Z, wherein Ar^2 is defined herein, a is 0 or 1, Z is –OH or aryl, and the Ar^2, –CH=CH-, and aryl moieties may be optionally substituted as suggested in the publication.

[0059] In a preferred embodiment of the compounds according to paragraph [0057], R^1 is an aryl selected from phenyl, naphthyl, anthracenyl, and fluorenyl. In another preferred embodiment, R^1 is a heteroaryl selected from those recited in paragraph [0045]. Other preferred R^1 moieties include azolyls (*e.g.*, thiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, etc.), pyridyl, and pyridinyl. More preferably, R^1 is furanyl or thienyl.

[0060] In a preferred embodiment of all the compounds of the invention, R^2, R^3, and R^4 are all hydrogen. Also preferred are compounds in which Φ is $-NH_2$ or -OH.

[0061] In a preferred embodiment of the compounds of paragraphs [0057], [0059], and [0060], Y is Cy^2-X^1-, wherein

Cy^2 is hydrogen, cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted and each of which is optionally fused to one or two aryl or heteroaryl rings, or

to one or two saturated or partially unsaturated cycloalkyl or heterocyclic rings, and wherein any of the aforementioned rings are optionally substituted; and

X^1 is selected from the group consisting of a covalent bond, M^1-L^2-M^1, and L^2-M^2-L^2 wherein

L^2, at each occurrence, is independently selected from the group consisting of a chemical bond, C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl-(NH)-C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl-(S)-C_0-C_4-hydrocarbyl, and C_0-C_4-hydrocarbyl-(O)-C_0-C_4-hydrocarbyl, provided that L^2 is not a chemical bond when X^1 is M^1-L^2-M^1;

M^1, at each occurrence, is independently selected from the group consisting of -O-, -N(R^7)-, -S-, -S(O)-, $S(O)_2$-, -$S(O)_2N(R^7)$-, -$N(R^7)$-$S(O)_2$-, -C(O)-, -C(O)-NH-, –NH-C(O)-, -NH-C(O)-O–and -O-C(O)-NH-, -NH-C(O)-NH-,

R^7 is selected from the group consisting of hydrogen, C_1-C_6-hydrocarbyl, aryl, aralkyl, acyl, C_0-C_6-hydrocarbyl-heterocyclyl, and C_0-C_6-hydrocarbyl-heteroaryl, wherein the hydrocarbyl moieties are optionally substituted with –OH, -NH_2, -N(H)CH_3, –$N(CH_3)_2$, or halo; and

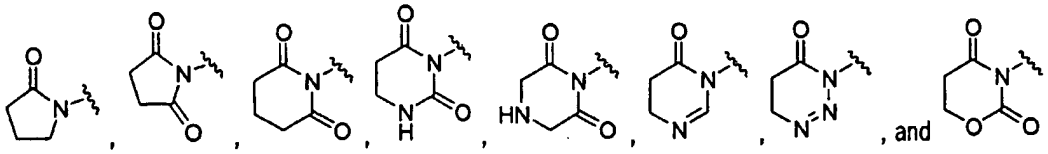
M^2 is selected from the group consisting of M^1, heteroarylene, and heterocyclylene, either of which rings optionally is substituted.

[0062] In some preferred embodiments according to paragraph [0061], the optional substituents of Cy^2 are selected from C_1-C_7-alkyl, C_1-C_7-alkoxy, halo, di-C_1-C_7-alkylamino-C_1-C_7-alkoxy and heteroaryl.

[0063] In some preferred embodiments according to paragraph [0061], X^1 is selected from the group consisting of a -N(Z)-C_0-C_7-alkyl-, -O-C_0-C_7-alkyl-, -C(H)=CH-C_0-C_7-alkyl-, -S-C_0-C_7-alkyl-, or -C_1-C_7-alkyl-, wherein Z is -H or -C_1-C_7-alkyl- optionally substituted with –OH, -NH_2, or halo.

[0064] In some embodiments of the compounds according to paragraph [0061], X^1 is a chemical bond. In some embodiments, X^1 is L^2-M^2-L^2, and M^2 is selected from the group consisting of -NH-, -$N(CH_3)$-, -S-, -C(O)-N(H)-, and -O-C(O)-N(H)-. In some embodiments, X^1 is L^2-M^2-L^2, where at least one occurrence of L^2 is a chemical bond. In other embodiments, X^1 is L^2-M^2-L^2, where at least one occurrence of L^2 is alkylene, preferably methylene. In still other embodiments, X^1 is L^2-M^2-L^2, where at least one occurrence of L^2 is alkenylene. In some embodiments, X^1 is M^1-L^2-M^1 and M^1 is selected from the group consisting of -NH-, -$N(CH_3)$-, -S-, and -C(O)-N(H)-. Preferred X^1 are selected from methylene, aminomethyl, and thiomethyl.

[0065] In some embodiments of the compounds according to paragraph [0061], Cy^2 is aryl or heteroaryl, *e.g.*, phenyl, pyridyl, imidazolyl, or quinolyl, each of which optionally is substituted. In some embodiments, Cy^2 is heterocyclyl, *e.g.*,



each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, Cy^2 has from one and three substituents independently selected from the group consisting of alkyl, alkoxy, amino, nitro, halo, haloalkyl, and haloalkoxy. Examples of preferred substituents include methyl, methoxy, fluoro, trifluoromethyl, trifluoromethoxy, nitro, amino, aminomethyl, and hydroxymethyl.

[0066] In some preferred embodiments of the compounds according to paragraph [0061], Cy^2 is phenyl, pyrimidinyl, benzimidazolyl or benzothiazolyl, each optionally substituted with one to three CH_3O-, dimethylamnio-ethoxy, chloro, fluoro and pyridinyl. In a more preferred embodiment, Cy^2 is phenyl substituted with one to three CH_3O-.

[0067] In some embodiments according to paragraph [0057], Y is $(V'\text{-}L^4)_t\text{-}V\text{-}L^3$-, wherein

L^3 is a direct bond, -C_1-C_6-hydrocarbyl, -$(C_1$-C_3-hydrocarbyl$)_{m1}$-X'-$(C_1$-C_3- hydrocarbyl$)_{m2}$, -NH-$(C_0$-C_3-hydrocarbyl), (C_1-C_3- hydrocarbyl)-NH-, or -NH-(C_1-C_3- hydrocarbyl)-NH-;

m1 and m2 are independently 0 or 1;

X' is -N(R^{21})-, -C(O)N(R^{21})-, N(R^{21})C(O)-, -O-, or -S-;

R^{21} is -H, V"-(C_1-C_6-hydrocarbyl)$_a$;

L^4 is (C_1-C_6-hydrocarbyl)$_a$-M-(C_1-C_6-hydrocarbyl)$_b$;

a and b are independently 0 or 1;

M is -NH-, -NHC(O)-, -C(O)NH-, -C(O)-, -SO_2-, -$NHSO_2$-, or -SO_2NH-

V, V', and V" are independently selected from cycloalkyl, heterocyclyl, aryl, and heteroaryl;

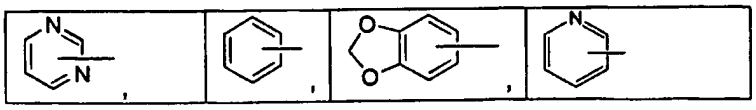
t is 0 or 1.

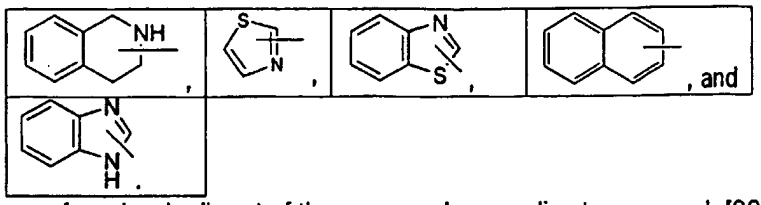
[0068] In some embodiments according to paragraph [0067], Y is V-L^3, wherein

L^3 is -NH-CH- or –CH-NH-;

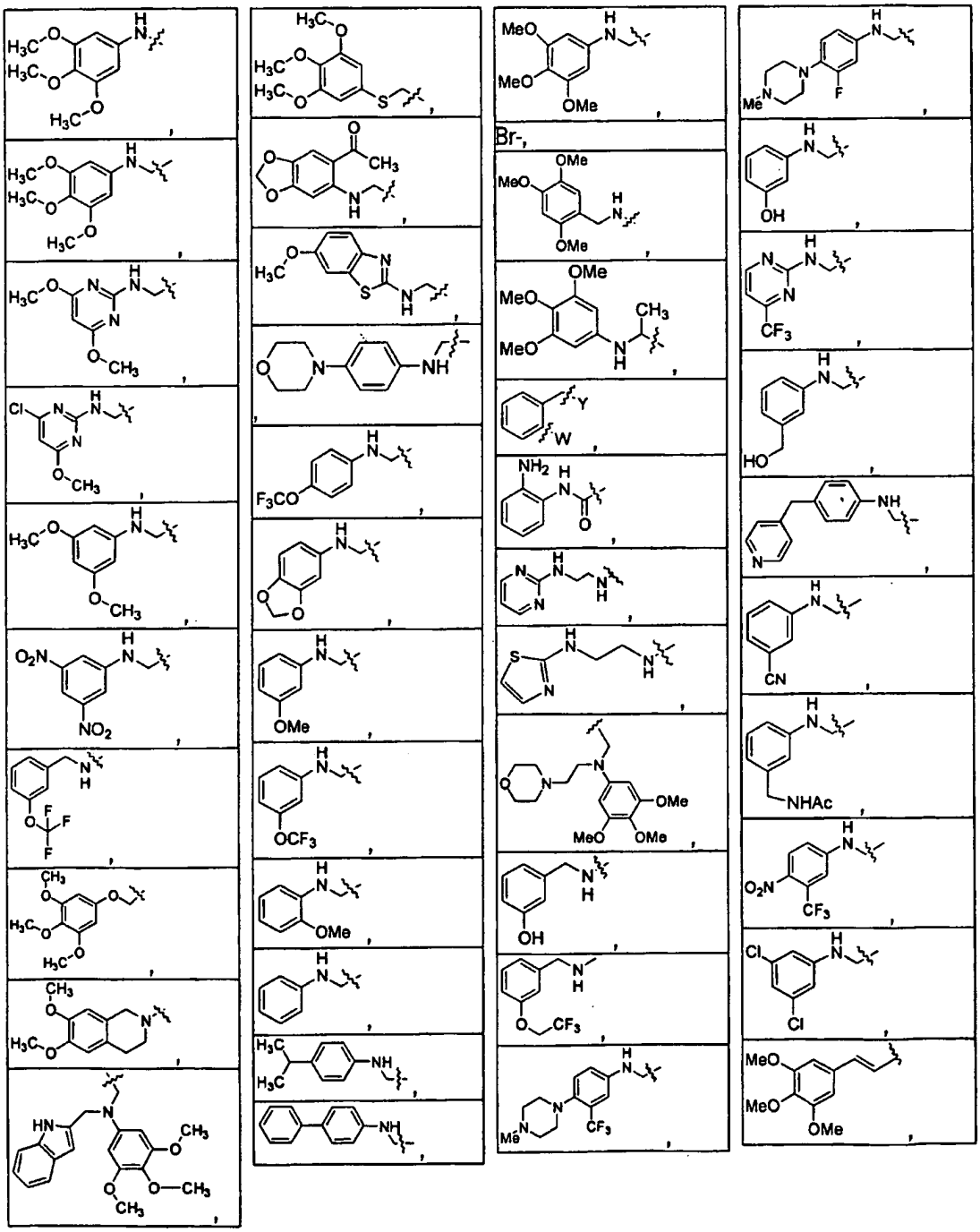
V is phenyl optionally substituted with from 1 to 3 moieties independently selected from halo, hydroxy, C_1-C_6-hydrocarbyl, C_1-C_6-hydrocarbyl-oxy or -thio (particularly methoxy or methylthio), wherein each of the hydrocarbyl moieties are optionally substituted with one or more moieties independently selected from halo, nitro, nitroso, formyl, acetyl, amino, sulfonamido, and cyano.

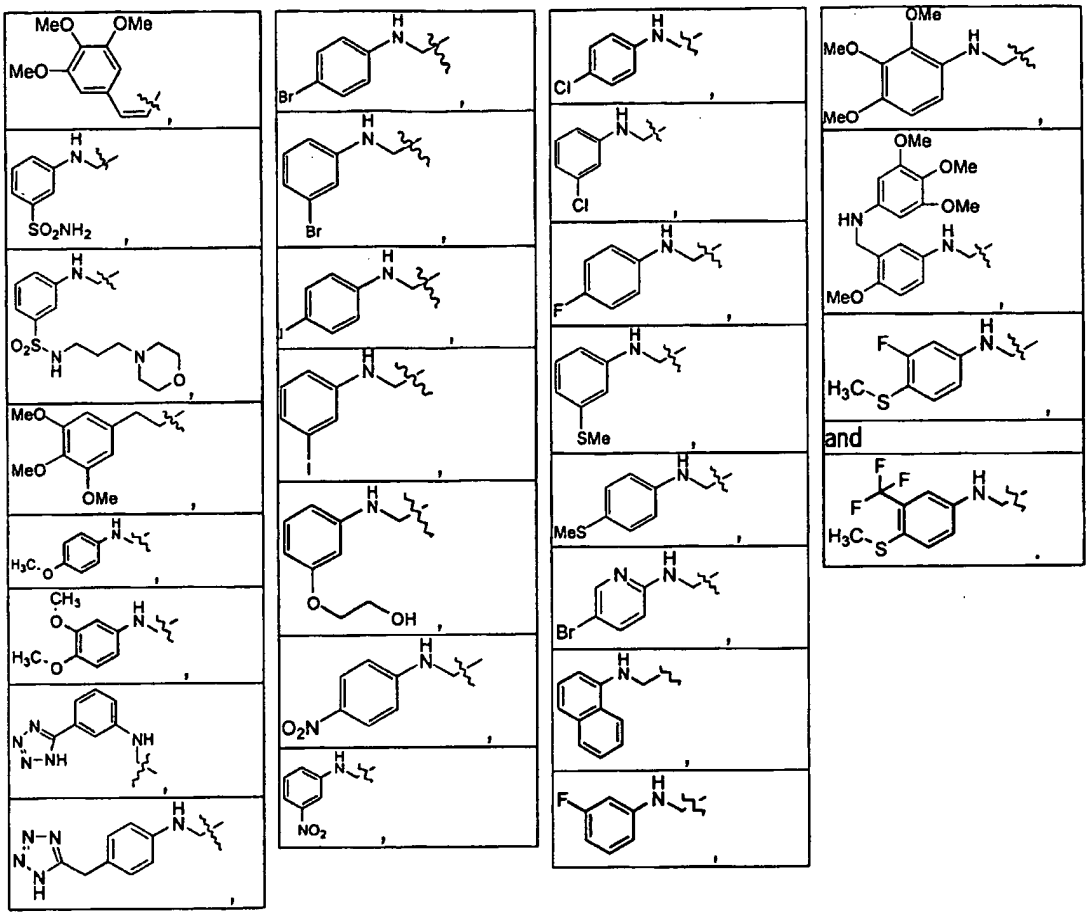
[0069] In some preferred embodiments of the compound according to paragraph [0067], V is an optionally substituted ring moiety selected from:





[0070] In another preferred embodiment of the compounds according to paragraph [0057], Y is selected from:,





[0071] In other embodiments of the compounds according to paragraph [0057],

X^1 is selected from $-CH_2-$, $-NH-CH_2-$, and $-S-CH_2-$; and

Cy^2 is monocyclic or fused bicyclic aryl or heteroaryl optionally substituted with one to three substituents selected from CH_3-, CH_3O-, phenyl optionally substituted with one to three CH_3O-, morphylinyl, morphylinyl-C_1-C_3-alkoxy, cyano, and $CH_3C(O)NH-$.

[0072] In other embodiments of the compounds according to paragraph [0057],

X^1 is selected from $-OCH_2$, $-CH_2O-$, $-CH_2-NH_2-$, and $-CH_2S-$; and

Cy^2 is monocyclic or fused bicyclic aryl or heteroaryl optionally substituted with one to three substituents selected from CH_3-, CH_3O-, phenyl optionally substituted with one to three CH_3O-, morphylinyl, morphylinyl-C_1-C_3-alkoxy, cyano, and $CH_3C(O)NH-$.

[0073] In one embodiment according to paragraph [0071], Cy^2 is phenyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, thienyl, tetrahydroquinozolinyl, or 1,3-dihydroquinazoline-2,4-dione, each optionally substituted with one to three CH_3O-. More preferably, Cy^2 is phenyl substituted with one to three CH_3O-.

[0074] In yet other embodiments of the compound according to paragraph [0057],

Cy^2 is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings optionally is substituted, provided that when Cy^2 is a cyclic moiety having -C(O)-, -C(S)-, -S(O)-, or $-S(O)_2-$ in the ring, then Cy^2 is not additionally substituted with a group comprising an aryl or heteroaryl ring; and

X^1 is selected from the group consisting of a chemical bond, L^3, W^1-L^3, L^3-W^1, W^1-L^3-W^1, and L^3-W^1-L^3, wherein

W^1, at each occurrence, is S, O, or $N(R^9)$, where R^9 is selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl; and

L^3 is C_1-C_4 alkylene, C_2-C_4 alkenylene, or C_2-C_4 alkynylene.

[0075] Preferably in the compounds according to paragraph [0074], X^2 is selected from the group consisting of L^3, W^1-L^3, L^3-W^1, W^1-L^3-W^1, and L^3-W^1-L^3.

[0076] In some embodiments of the compounds according to paragraph [0074], X^1 is a chemical bond. In other embodiments, X^1 is a non-cyclic hydrocarbyl. In some such embodiments, X^1 is alkylene, preferably methylene or ethylene. In other such embodiments, X^1 is alkenylene. In still other such embodiments, one carbon in the hydrocarbyl chain is replaced with -NH- or -S-, and in others with a –O-. In some preferred embodiments, X^1 is W^1-L^3-W^1 and W^1 is -NH- or $-N(CH_3)-$.

[0077] In some embodiments of the compounds according to paragraph [0074], Cy^2 is cycloalkyl, preferably cyclohexyl. In other embodiments, Cy^2 is aryl or heteroaryl, *e.g.*, phenyl, pyridyl, pyrimidyl, imidazolyl, thiazolyl, oxadiazolyl, quinolyl, or fluorenyl, each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, the cyclic moiety of Cy^2 is fused to a benzene ring. In some embodiments, Cy^2 has from one to three substituents independently selected from the group consisting of alkyl, alkoxy, aryl, aralkyl, amino, halo, haloalkyl, and hydroxyalkyl. Examples of preferred substituents include methyl, methoxy, fluoro, trifluoromethyl, amino, nitro, aminomethyl, hydroxymethyl, and phenyl. Some other preferred substituents have the formula $-K^1$-$N(H)(R^{10})$, wherein

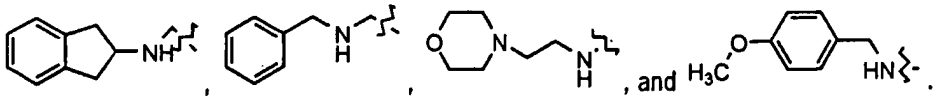
K^1 is a chemical bond or C_1-C_4 alkylene;

R^{10} is selected from the group consisting of Z' and $-Ak^2$-Z', wherein

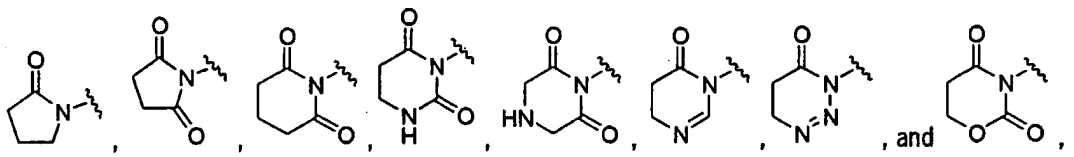
Ak^2 is C_1-C_4 alkylene; and

Z' is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings.

[0078] Examples of such preferred substituents according to paragraph [0077] include



[0079] In some embodiments of the compounds according to paragraph [0074], Cy^2 is heterocyclyl, *e.g.*,



each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, the heterocycle of Cy^2 is fused to a benzene ring.

[0080] In certain preferred embodiments of the compound according to paragraph [0057], Cy^2-X^1- is collectively selected from the group consisting of

a) A_1-L_1-B_1-, wherein A_1 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_1 is $-(CH_2)_{0-1}NH(CH_2)_{0-1}$-, -NHC(O)-, or -$NHCH_2$-; and wherein B_1 is phenyl or a covalent bond;

b) A_2-L_2-B_2-, wherein A_2 is $CH_3(C{=}CH_2)$-, optionally substituted cycloalkyl, optionally substituted alkyl, or optionally substituted aryl; wherein L_2 is –C≡C-; and wherein B_2 is a covalent bond;

c) A_3-L_3-B_3-, wherein A_3 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_3 is a covalent bond; and wherein B_3 is $-CH_2NH$-;

d) A_4-L_4-B_4-, wherein A_4 is an optionally substituted aryl; wherein L_4 is –$NHCH_2$-; and wherein B_4 is a thienyl group;

e) A_5-L_5-B_5-, wherein A_5 is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_5 is a covalent bond; and wherein B_5 is -SCH_2-;

f) morpholinyl-CH_2-

g) optionally substituted aryl;

h) A_6-L_6-B_6-, wherein A_6 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_6 is a covalent bond; and wherein B_6 is –$NHCH_2$-;

i) A_7-L_7-B_7-, wherein A_7 is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_7 is a covalent bond; and wherein B_7 is –CH_2-;

j) optionally substituted heteroaryl or optionally substituted heterocyclyl;

k) A_8-L_8-B_8-, wherein A_8 is optionally substituted phenyl; wherein L_8 is a covalent bond; and wherein B_8 is -O-;

l) A_9-L_9-B_9-, wherein A_9 is an optionally substituted aryl; wherein L_9 is a covalent bond; and wherein B_9 is a furan group;

m) A_{10}-L_{10}-B_{10}-, wherein A_{10} is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{10} is $-CH(CH_2CH_3)-$; and wherein B_{10} is $-NHCH_2-$;

n) A_{11}-L_{11}-B_{11}-, wherein A_{11} is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{11} is a covalent bond; and wherein B_{11} is $-OCH_2-$;

o) A_{12}-L_{12}-B_{12}-, wherein A_{12} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{12} is -NHC(O)-; and wherein B_{12} is –N(optionally substituted aryl)CH_2-;

p) A_{13}-L_{13}-B_{13}-, wherein A_{13} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{13} is a covalent bond; and wherein B_{13} is -NHC(O)-;

q) A_{14}-L_{14}-B_{14}-, wherein A_{14} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{14} is-NHC(O)(optionally substituted heteroaryl); and wherein B_{14} is –S-S-;

r) $F_3CC(O)NH$-;

s) A_{15}-L_{15}-B_{15}-, wherein A_{15} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{15} is-$(CH_2)_{0-1}$NH(optionally substituted heteroaryl)-; and wherein B_{15} is $-NHCH_2-$;

t) A_{16}-L_{16}-B_{16}-, wherein A_{16} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{16} is a covalent bond; and wherein B_{16} is –N(optionally substituted alkyl)CH_2-; and

u) A_{17}-L_{17}-B_{17}-, wherein A_{17} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{17} is a covalent bond; and wherein B_{17} is –(optionally substituted aryl-$CH_2)_2$-N-.

[0081] In another preferred embodiment of the compounds according to paragraph [0057], Cy^2-X^1- is collectively selected from the group consisting of

a) D_1-E_1-F_1-, wherein D_1 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_1 is $-CH_2-$ or a covalent bond; and wherein F_1 is a covalent bond;

b) D_2-E_2-F_2-, wherein D_2 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_2 is $-NH(CH_2)_{0-2}$-; and wherein F_2 is a covalent bond;

c) D_3-E_3-F_3-, wherein D_3 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_3 is $-(CH_2)_{0-2}NH-$; and wherein F_3 is a covalent bond;

d) D_4-E_4-F_4-, wherein D_4 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_4 is $-S(CH_2)_{0-2}-$; and wherein F_4 is a covalent bond;

e) D_5-E_5-F_5-, wherein D_5 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_5 is $-(CH_2)_{0-2}S-$; and wherein F_5 is a covalent bond; and

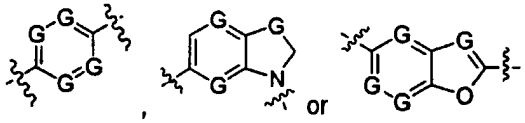
f) D_6-E_6-F_6-, wherein D_6 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_6 is $-NH(CH_2)_{0-2}NH-$; and wherein F_6 is a covalent bond.

[0082] In some embodiments according to paragraphs [0057] and [0059]-[0074], R^2 to R^4 are independently hydrogen, $-NH_2$, nitro, furanyl, chloro, fluoro, butyl, trifluoromethyl, bromo, thienyl, phenyl, $-CHCHC(O)-NH_2$, $-C{\equiv}CCH_2-R^9$ wherein R^9 is hydrogen, C_1-C_7-alkyl, hydroxy, amino, or C_1-C_7-alkoxy.

[0083] In some preferred embodiments of the compound according to paragraphs [0057] and [0059]-[0082], q is 0 and X^1 is independently selected from the group consisting of $-NH-CH_2-$, $-S-CH_2-$ and $-CH_2-$.

[0084] In some preferred embodiments of the compound according to paragraphs [0057] and [0059]-[0082], q is 0 and X^1 is independently selected from the group consisting of $-OCH_2$, $-CH_2O-$, $-CH_2-NH_2-$, and $-CH_2S-$.

[0085] In some embodiments of the compound according to paragraphs [0057] and [0059]-[0083], the compound has Ar^2 of formula



or

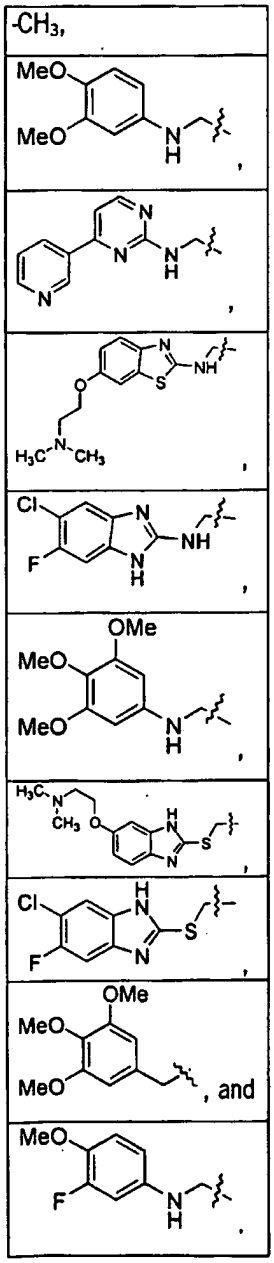
wherein G, at each occurrence, is independently N or C, and C is optionally substituted.

[0086] In some embodiments of the compounds according to paragraph [0085], G at each occurrence is $C(R^8)$, wherein R^8 is selected from the group consisting of hydrogen and C_1-C_7-alkyl. In some more preferred embodiments, G is -CH-.

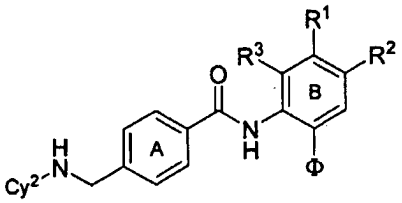
[0087] In some preferred embodiments, the compounds according to paragraph [0085] are those wherein Ar^2 is selected from the group consisting of phenylene, benzofuranylene and indolinylene.

[0088] In some preferred embodiments, Cy^2 is aryl or heteroaryl, each of which is optionally substituted. More preferably, Cy^2 is phenyl, pyrimidinyl, benzimidazolyl or benzothiazolyl, each of which is optionally substituted. Preferred substituents of Cy^2 are from one to three substituents independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkoxy, halo, di-C_1-C_7-alkylamino-C_1-C_7-alkoxy and heteroaryl. More preferably, the substituents of Cy^2 are selected from methyl, methoxy, fluoro, chloro, pyridinyl and dimethylamino-ethoxy.

[0089] In some preferred embodiments, the moiety formed by Cy^2-X^1 is selected from the following:



[0090] In a preferred embodiment, the compounds of paragraph [0061] are represented by the general formula (2):



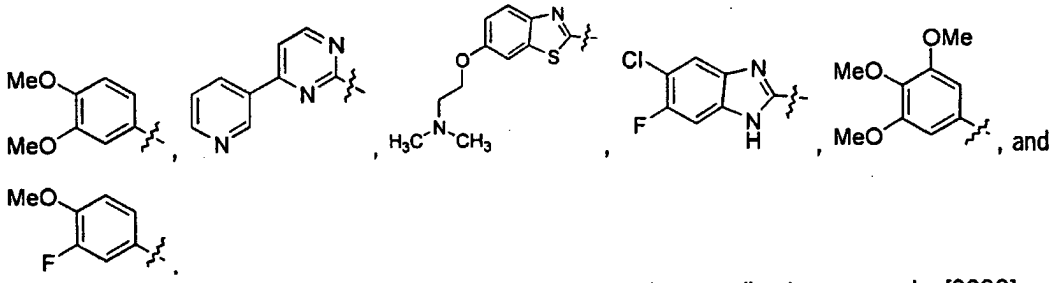
(2)

or a pharmaceutically acceptable salt thereof, wherein

R^2 and R^3 are independently selected from the group consisting of hydrogen, trifluoromethyl, butyl, -$(CH_2)_3$-OH, chloro, fluoro, amino, phenyl, thienyl, furanyl, -CH=CHC(O)NH_2, -C≡CCH_2-OH, -C≡CCH_2-OCH_3; and

the A ring is optionally further substituted with from 1 to 3 substituents independently selected from methyl, hydroxy, methoxy, halo, and amino.

[0091] In some preferred embodiments, the compounds according to paragraph [0090] are those in which Cy^2 is selected from:

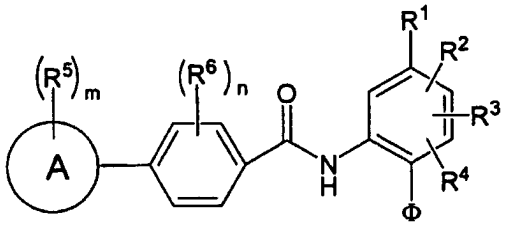


, and

[0092] In other preferred embodiments of the compounds according to paragraphs [0090] and [0091], the A ring is not further substituted.

[0093] In another preferred embodiment of the compounds according to paragraphs [0090] - [0092], R^2 and R^3 are both -H.

[0094] In another embodiment of this aspect, the invention comprises compounds of the general formula (3):



(3)

or a pharmaceutically acceptable salt or *in vivo* hydrolyzable ester or amide thereof; wherein:

Φ is $-NH_2$ or –OH;

Ring *A* is a heterocyclyl, wherein if said heterocyclyl contains an -NH- moiety that nitrogen is optionally substituted by a group selected from K;

R^5 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{1-6}-alkanoyl, C_{1-6}-alkanoyloxy, *N*-(C_{1-6}-alkyl)amino, *N*,*N*-(C_{1-6}-alkyl)$_2$amino, C_{1-6}-alkanoylamino, *N*-(C_{1-6}-alkyl)carbamoyl, *N*,*N*-(C_{1-6}-alkyl)$_2$carbamoyl, C_{1-6}-alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}-alkoxycarbonyl, *N*-(C_{1-6}-alkyl)sulphamoyl, *N*,*N*-(C_{1-6}-alkyl)$_2$sulphamoyl, aryl, aryloxy, arylC_{1-6}-alkyl, heterocyclic group, (heterocyclic group)C_{1-6}-alkyl, or a group (B-E-); wherein R^5, including group (B-E-), is optionally substituted on carbon by one or more W; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen is optionally substituted by J;

W is halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{1-6}-alkanoyl, C_{1-6}-alkanoyloxy, *N*-(C_{1-6}-alkyl)amino, *N*,*N*-(C_{1-6}-alkyl)$_2$amino, C_{1-6}-alkanoylamino, *N*-(C_{1-6}-alkyl)carbamoyl, *N*,*N*-(C_{1-6}-alkyl)$_2$carbamoyl, C_{1-6}-alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}-alkoxycarbonyl, *N*-(C_{1-6}-alkyl)sulphamoyl, *N*,*N*-(C_{1-6}-alkyl)$_2$sulphamoyl, or a group (B'-E'-); wherein W, including group (B'-E'-), is optionally substituted on carbon by one or more Y;

Y and *Z* are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{1-6}-alkanoyl, C_{1-6}-alkanoyloxy, *N*-(C_{1-6}-alkyl)amino, *N*,*N*-(C_{1-6}-alkyl)$_2$amino, C_{1-6}-alkanoylamino, *N*-(C_{1-6}-alkyl)carbamoyl, *N*,*N*-(C_{1-6}-alkyl)$_2$carbamoyl, C_{1-6}-alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}-alkoxycarbonyl, *N*-(C_{1-6}-alkyl)sulphamoyl or *N*,*N*-(C_{1-6}-alkyl)$_2$sulphamoyl;

G, J and K are independently selected from C_{1-8}-alkyl, C_{1-8}-alkenyl, C_{1-8}-alkanoyl, C_{1-8}-alkylsulphonyl, C_{1-8}-alkoxycarbonyl, carbamoyl, *N*-(C_{1-8}-alkyl)carbamoyl, *N*,*N*-(C_{1-8}-alkyl)carbamoyl, benzyloxycarbonyl, benzoyl, phenylsulphonyl, aryl, arylC_{1-6}-alkyl or (heterocyclic group)C_{1-6}-alkyl; wherein G, J, and K are optionally substituted on carbon by one or more Q; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen is optionally substituted by hydrogen or C_{16}alkyl;

Q is halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{1-6}-alkanoyl, C_{1-6}-alkanoyloxy, *N*-(C_{1-6}-alkyl)amino, *N*,*N*-(C_{1-6}-alkcyl)$_2$amino, C_{1-6}-alkanoylamino, *N*-(C_{1-6}-alkyl)carbamoyl, *N*,*N*-(C_{1-6}-alkyl)$_2$carbamoyl, C_{1-6}-alkylS(O)$_a$

wherein a is 0 to 2, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkoxycarbonylamino, *N*-(C_{1-6}-alkyl)sulphamoyl, *N*,*N*-(C_{1-6}-alkyl)$_2$sulphamoyl, aryl, aryloxy, aryl C_{1-6}-alkyl, arylC_{1-6}-alkoxy, heterocyclic group, (heterocyclic group)C_{1-6}-alkyl, (heterocyclic group)C_{1-6}-alkoxy, or a group (B"-E"-); wherein Q, including group (B"-E"-), is optionally substituted on carbon by one or more Z;

B, B' and B" are independently selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkylC_{1-6}-alkyl, aryl, arylC_{1-6}-alkyl, heterocyclic group, (heterocyclic group)C_{1-6}-alkyl, phenyl or phenylC_{1-6}-alkyl; wherein B, B' and B" is optionally substituted on carbon by one or more D; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen is optionally substituted by a group selected from G;

E, E' and E" are independently selected from -N(R^a)-, -O-, -C(O)O-, -OC(O)-, -C(O)-, -N(R^a)C(O)-, -N(R^a)C(O)N(R^b)-, -N(R^a)C(O)O-, -OC(O)N(R^a)-, -C(O)N(R^a)-, S(O)$_r$, -SO_2N(R^a)-, -N(R^a)SO_2- wherein R^a and R^b are independently selected from hydrogen or C_{1-6}-alkyl optionally substituted by one or more F and r is 0-2;

D and F are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{1-6}-alkanoyl, C_{1-6}-alkanoyloxy, *N*-(C_{1-6}-alkyl)amino, *N*,*N*-(C_{1-6}-alkyl)$_2$amino, C_{1-6}-alkanoylamino, *N*-(C_{1-6}-alkyl)carbamoyl, *N*,*N*-(C_{1-6}-alkyl)$_2$carbamoyl, C_{1-6}-alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}-alkoxycarbonyl, *N*-(C_{1-6}-alkyl)sulphamoyl or *N*,*N*-(C_{1-6}-alkyl)$_2$sulphamoyl;

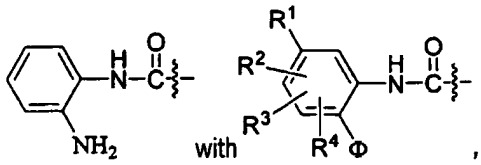
m is 0, 1, 2, 3 or 4; wherein the values of R^5 may be the same or different;

R^6 is halo;

n is 0, 1 or 2; wherein the values of R^6 may be the same or different; and

R^1, R^2, R^3, and R^4 are as defined in paragraph [0057].

[0095] In the embodiments of the compounds according to paragraph [0094], R^1, R^2, R^3, and R^4 are as defined in paragraphs [0059] and [0060]. In other preferred embodiments, the compounds according to paragraph [0094] are the compounds of WO 03/087057, particularly those of Tables 1-8 and 13, modified by replacing the terminal moiety:



wherein Φ, R^1, R^2, R^3, and R^4 are as defined in accordance with paragraphs [0057], and preferably [0059] and [0060].

[0096] The definitions in paragraphs [0097] - [0104] apply to R^5 and R^6 in paragraph [0094] and supplement the definitions in paragraphs [0031] - [0053]. To the extent there are any inconsistencies between the definitions in paragraphs [0031] - [0053] and in paragraphs [0097] - [0104], the definitions in paragraphs [0097] - [0104] shall take precedence for the compounds of paragraph [0094] only.

[0097] "Alkyl" includes both straight and branched chain alkyl groups. For example, "C_{1-8}-alkyl" and "C_{1-6}-alkyl" includes methyl, ethyl, propyl, isopropyl, pentyl, hexyl, heptyl, and t-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight-chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only.

[0098] The term "halo" refers to fluoro, chloro, bromo and iodo.

[0099] Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

[0100] A "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a ring sulphur atom is optionally oxidized to form the S-oxide(s). Preferably a "heterocyclyl" is a saturated, partially saturated or unsaturated, monocyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen or a 8-10 membered bicyclic ring which may, unless otherwise specified, be carbon or nitrogen linked, wherein a ring sulphur atom is optionally oxidized to form S-oxide(s). Examples and suitable values of the term "heterocyclyl" are thiazolidinyl, pyrrolidinyl, 1,3-benzodioxolyl, 1,2,4-oxadiazolyl, 2-azabicyclo[2.2.1]heptyl, morpholinyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, piperidinyl, piperazinyl, thiomorpholinyl, 1,3-dioxolanyl, homopiperazinyl, thienyl, pyrrolyl, pyrazolyl, oxadiazolyl, tetrazolyl, oxazolyl, thienopyrimidinyl, thienopyridinyl, thieno[3,2d]pyrimidinyl, 1,3,5-triazinyl, purinyl, 1,2,3,4-tetrahydroquinolinyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzothienyl, benzofuranyl, indazolyl, quinazolinyl, cinnolinyl, phthalazinyl, quinoxalinyl, napthyridinyl, benzotriazolyl, pyrrolothienyl, imidazothienyl, isoxazolyl, imidazolyl, thiadiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, indolyl, pyrimidyl, thiazolyl, pyrazinyl, pyridazinyl, pyridyl, quinolyl, quinazolinyl, and 1-isoquinolinyl.

[0101] A "heterocyclic group" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a CH_2 group is optionally replaced by a C(O), and wherein a ring sulphur atom is optionally oxidized to form the S-

oxide(s). Preferably a "heterocyclic group" is a saturated, partially saturated or unsaturated, monocyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen or a 9 or 10 membered bicyclic ring which may, unless otherwise specified, be carbon or nitrogen linked, wherein a CH_2 group is optionally replaced by a C(O), and wherein a ring sulphur atom is optionally oxidized to form S-oxide(s). Examples and suitable values of the term "heterocyclic group" are pyrrolidinyl, 2-pyrrolidonyl 2,5-dioxopyrrolidinyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-triazolinyl, oxazolidinyl, 2-oxazolidonyl, 5,6-dihydro-uracilyl, 1,3-benzodioxolyl, 1,2,4-oxadiazolyl, 2-azabicyclo[2.2.1]heptyl, morpholinyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, piperidinyl, piperazinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, 1,3-dioxolanyl, homopiperazinyl, thiophenyl, thienopyridinyl, thienopyrimidinyl, thieno[3,2d]pyrimidinyl, 1,3,5-triazinyl, purinyl, quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, tetrahydroisoquinolinyl, imidazolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzothiophenyl, benzofuranyl, indazolyl, quinazolinyl, cinnolinyl, phthalazinyl, quinoxalinyl, napthyridinyl, oxazolyl, isoxazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, indolyl, isoindolyl, pyrimidinyl, thiazolyl, pyrazolyl, 3-pyrrolinyl, pyrazinyl, pyridazinyl, pyridinyl, pyridonyl, pyrimidonyl and 1-isoquinolinyl.

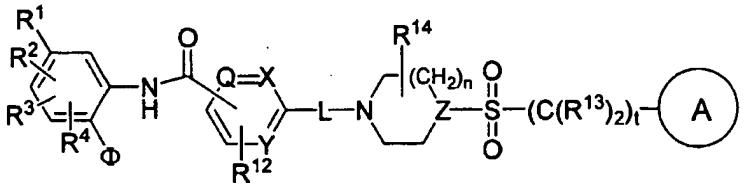
[0102] An "aryl" group is, for example, phenyl, indenyl, indanyl, naphthyl, tetrahydronaphthyl or fluorenyl, preferably phenyl.

[0103] An example of "C_{1-6}-alkanoyloxy" is acetoxy. Examples of "C_{1-8}-alkoxycarbonyl", "C_{1-6}-alkoxycarbonyl" and C_{1-4}-alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, *N*- and *t*-butoxycarbonyl. Examples of C_{2-6}-alkynyl are ethynyl and 2-propynyl. Examples of "C_{1-6}-alkoxy" include methoxy, ethoxy and propoxy. Examples of "C_{1-6}-alkanoylamino" and C_{1-3}-alkanoylamino include formamido, acetamido and propionylamino. Examples of "C_{1-6}-alkyl$S(O)_a$ wherein a is 0 to 2" include C_{1-6}-alkylsulphonyl, C_{1-3}-alkyl$S(O)_a$, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsuiphonyl. Examples of "C_{1-8}-alkanoyl", "C_{1-6}-alkanoyl" and C_{1-4}-alkanoyl include C_{1-3}-alkanoyl, propionyl and acetyl. Examples of "*N*-C_{1-6}-alkylamino" and *N*-(C_{1-3}-alkyl)amino include methylamino and ethylamino. Examples of "*N*,*N*-(C_{1-6}-alkyl)$_2$amino" and *N*,*N*-(C_{1-2}-alkyl)$_2$amino include di-*N*-methylamino, di-(*N*-ethyl)amino, di-(*N*-butyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-8}-alkenyl" are C_{1-6}-alkenyl and C_{2-3}-alkenyl, and include vinyl, allyl, and 1-propenyl. Examples of "*N*-(C_{1-3}-alkyl)sulphamoyl" and "*N*-(Ci_5alkyl)sulphamoyl" are *N*-(C_{1-3}-alkyl)sulphamoyl, *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}-alkyl)$_2$sulphamoyl" are *N*,*N*-(C_{1-3}-alkyl)$_2$sulphamoyl, *N*,*N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "N-(C_{1-8}-alkyl)carbamoyl" and "*N*-(C_{1-6}-alkyl)carbamoyl" are *N*-(C_{1-4}-alkyl)carbamoyl, *N*-(C_{1-3}-alkyl)carbamoyl, methylaminocarbonyl, and ethylaminocarbonyl. Examples of "*N*,*N*-(C_{1-8}-alkyl)$_2$carbamoyl" and "*N*,*N*-(C_{1-6}-alkyl)$_2$carbamoyl" are *N*,*N*-(C_{1-4}-alkyl)$_2$carbamoyl, *N*,*N*-(C_{1-2}-alkyl)$_2$carbamoyl, dimethylaminocarbonyl and

methylethylaminocarbonyl. Examples of "(heterocyclic group)C_{1-6}-alkyl" include piperidin-1-ylmethyl, piperidin-1-ylethyl, piperdin-1-ylpropyl, pyridylmethyl, 3-morpholinopropyl, 2-morpholinoethyl and 2-pyrimid-2-ylethyl. Examples of "(heterocyclic group)C_{1-6}-alkoxy" include (heterocyclic group)methoxy, (heterocyclic group)ethoxy and (heterocyclic group)propoxy. Examples of "arylC_{1-6}-alkyl" include benzyl, 2-phenylethyl, 2-phenylpropyl and 3-phenylpropyl. Examples of "aryloxy" include phenoxy and naphthyloxy. Examples of "C_{3-8}-cycloalkyl" include cyclopropyl and cyclohexyl. Examples of "C_{3-8}-cycloalkylC_{1-6}-alkyl" include cyclopropylmethyl and 2-cyclohexylpropyl. Examples of "C_{1-6}-alkoxycarbonylamino" include methoxycarbonylamino and t-butoxycarbonylamino.

[0104] Composite terms are used to describe groups comprising more than one functionality such as arylC_{1-4}-alkyl. Such terms are to be interpreted as is understood by a person skilled in the art. For example arylC_{1-6}-alkyl comprises C_{1-6}-alkyl substituted by aryl and such a group includes benzyl, 2-phenylethyl, 2-phenylpropyl and 3-phenylpropyl.

[0105] In another embodiment of this aspect, the invention comprises compounds of the following general formula (4):



(4)

the N-oxide forms, the pharmaceutically acceptable addition salts and the stereo-chemically isomeric forms thereof, wherein

Φ is $-NH_2$ or $-OH$;

n is 0,1, 2 or 3, wherein when n is 0 then a direct bond is intended;

t is 0, 1, 2, 3 or 4, wherein when t is 0 then a direct bond is intended;

Q, X, Y, and Z are independently N or CH;

R^1 is H or as defined in paragraph [0057],

R^2, R^3, and R^4 are as defined in paragraph [0057];

R^{12} is hydrogen, halo, hydroxy, amino, nitro, C_{1-6}-alkyl, C_{1-6}-alkyloxy, trifluoromethyl, di(C_{1-6}-alkyl)amino, hydroxyamino and naphthalenylsulfonylpyrazinyl;

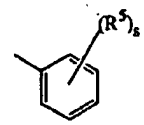
-L- is a direct bond or a bivalent radical selected from C_{1-6}-alkanediyl, amino, carbonyl and aminocarbonyl;

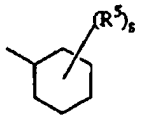
each R^{13} is a hydrogen atom, wherein when t is 2, 3, or 4 one of the R^{13} is optionally aryl;

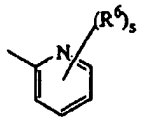
R^{14} is hydrogen, hydroxy, amino, hydroxyC_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkyloxy,arylC_{1-6}-alkyl, aminocarbonyl, hydroxycarbonyl, aminoC_{1-6}-alkyl, aminocarbonylC_{1-6}-alkyl,

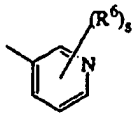
hydroxycarbonylC_{1-6}-alkyl, hydroxyaminocarbonyl, C_{1-6}-alkyloxycarbonyl, C_{1-6}-alkylaminoC_{1-6}-alkyl or di(C_{1-6}-alkyl)aminoC_{1-6}-alkyl;

Ring A is selected from


(a-1)


(a-2)


(a-3)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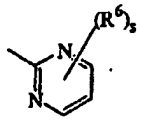
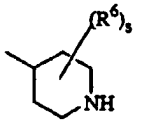

(a-5)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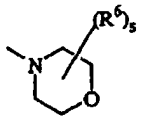
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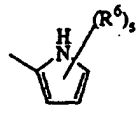
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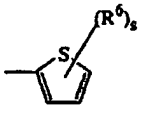
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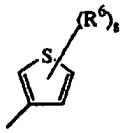
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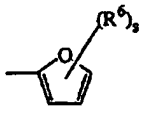
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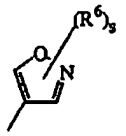
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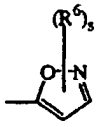
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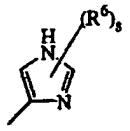
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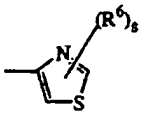
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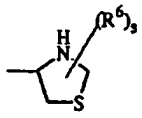
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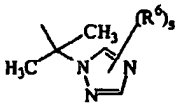
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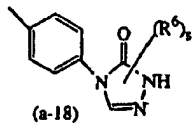
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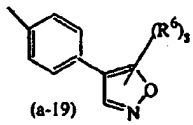
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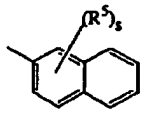
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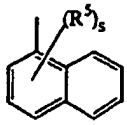
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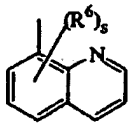
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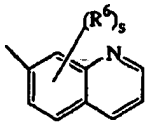
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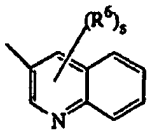
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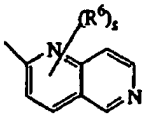
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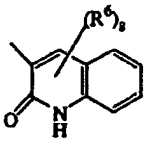
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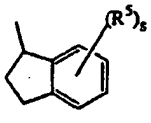
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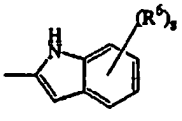
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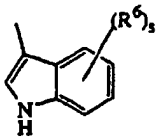
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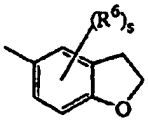
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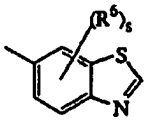
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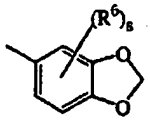
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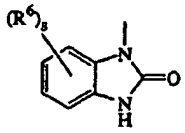
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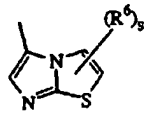
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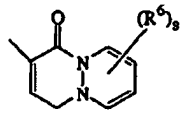
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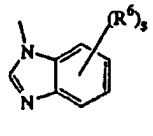
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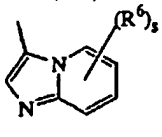
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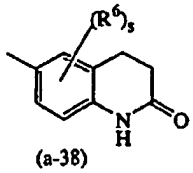
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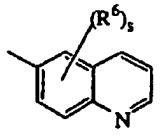
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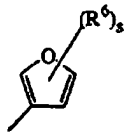
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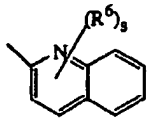
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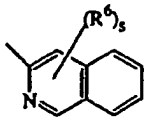
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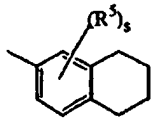
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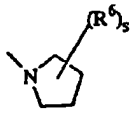
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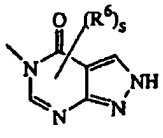
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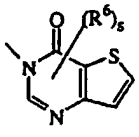
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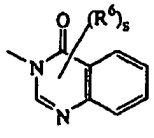
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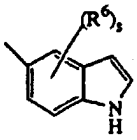
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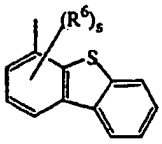
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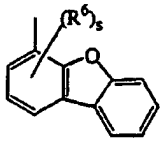
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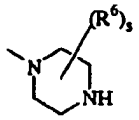

(a-51)

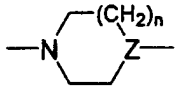
wherein each s is independently 0, 1, 2, 3, 4 or 5;

R^5 and R^6 are independently selected from hydrogen; halo; hydroxy; amino; nitro; trihaloC_{1-6}-alkyl; trihaloC_{1-6}-alkyloxy; C_{1-6}-alkyl; C_{1-6}-alkyl substituted with aryl and C_{3-10}-cycloalkyl; C_{1-6}-alkyloxy; C_{1-6}-alkyloxyC_{1-6}-alkyloxy; C_{1-6}-alkylcarbonyl; C_{1-6}-alkyloxycarbonyl; C_{1-6}-alkylsulfonyl; cyanoC_{1-6}-alkyl; hydroxyC_{1-6}-alkyl; hydroxyC_{1-6}-alkyloxy; hydroxyC_{1-6}-alkylamino; aminoC_{1-6}-alkyloxy; di(C_{1-6}-alkyl)aminocarbonyl; di(hydroxyC_{1-6}-alkyl)amino; (aryl)(C_{1-6}-alkyl)amino; di(C_{1-6}-alkyl)aminoC_{1-6}-alkyloxy; di(C_{1-6}-alkyl)aminoC_{1-6}-alkylamino; di(C_{1-6}-alkyl)aminoC_{1-6}-alkylaminoC_{1-6}-alkyl; arylsulfonyl; arylsulfonylamino; aryloxy; aryloxyC_{1-6}-alkyl; arylC_{2-6}-alkenediyl; di(C_{1-6}-alkyl)amino; di(C_{1-6}-alkyl)aminoC_{1-6}-alkyl; di(C_{1-6}-alkyl)amino(C_{1-6}-alkyl)amino; di(C_{1-6}-alkyl)amino(C_{1-6}-alkyl)aminoC_{1-6}-alkyl; di(C_{1-6}-alkyl)aminoC_{1-6}-alkyl(C_{1-6}-alkyl)amino; di(C_{1-6}-alkyl)aminoC_{1-6}-alkyl(C_{1-6}-alkyl)aminoC_{1-6}-alkyl; aminosulfonylamino(C_{1-6}-alkyl)amino; aminosulfonylamino(C_{1-6}-alkyl)aminoC_{1-6}-alkyl; di(C_{1-6}-alkyl)aminosulfonylamino(C_{1-6}-alkyl)amino; di(C_{1-6}-alkyl)aminosulfonylamino(C_{1-6}-alkyl)aminoC_{1-6}-alkyl; cyano; thiophenyl; thiophenyl substituted with di(C_{1-6}-alkyl)aminoC_{1-6}-alkyl(C_{1-6}-alkyl)aminoC_{1-6}-alkyl, di(C_{1-6}-alkyl)aminoC_{1-6}-alkyl, C_{1-6}-alkylpiperazinylC_{1-6}-alkyl, hydroxyC_{1-6}-alkylpiperazinylC_{1-6}-alkyl, hydroxyC_{1-6}-alkyloxyC_{1-6}-alkylpiperazinylC_{1-6}-alkyl,

di(C_{1-6}-alkyl)aminosulfonylpiperazinylC_{1-6}-alkyl, C_{1-6}-alkyloxypiperidinyl, C_{1-6}-alkyloxypiperidinylC_{1-6}-alkyl, morpholinylC_{1-6}-alkyl, hydroxyC_{1-6}-alkyl(C_{1-6}-alkyl)aminoC_{1-6}-alkyl, or di(hydroxyC_{1-6}-alkyl)aminoC_{1-6}-alkyl; furanyl; furanyl substituted with hydroxyC_{1-6}-alkyl; benzofuranyl; imidazolyl; oxazolyl; oxazolyl substituted with aryl and C_{1-6}-alkyl; C_{1-6}-alkyltriazolyl; tetrazolyl; pyrrolidinyl; pyrrolyl; piperidinylC_{1-6}-alkyloxy; morpholinyl; C_{1-6}-alkylmorpholinyl; morpholinylC_{1-6}-alkyloxy; morpholinylC_{1-6}-alkyl; morpholinylC_{1-6}-alkylamino; morpholinylC_{1-6}-alkylaminoC_{1-6}-alkyl; piperazinyl; C_{1-6}-alkylpiperazinyl; C_{1-6}-alkylpiperazinylC_{1-6}-alkyloxy; piperazinylC_{1-6}-alkyl; naphthalenylsulfonylpiperazinyl; naphthalenylsulfonylpiperidinyl; naphthalenylsulfonyl; C_{1-6}-alkylpiperazinylC_{1-6}-alkyl; C_{1-6}-alkylpiperazinylC_{1-6}-alkylamino; C_{1-6}-alkylpiperazinylC_{1-6}-alkylaminoC_{1-6}-alkyl; C_{1-6}-alkylpiperazinylsulfonyl; aminosulfonylpiperazinylC_{1-6}-alkyloxy; aminosulfonylpiperazinyl; aminosulfonylpiperazinylC_{1-6}-alkyl; di(C_{1-6}-alkyl)aminosulfonylpiperazinyl; di(C_{1-6}-alkyl)aminosulfonylpiperazinylC_{1-6}-alkyl; hydroxyC_{1-6}-alkylpiperazinyl; hydroxyC_{1-6}-alkylpiperazinylC_{1-6}-alkyl; C_{1-6}-alkyloxyperidinyl; C_{1-6}-alkyloxypiperidinylC_{1-6}-alkyl; piperidinylaminoC_{1-6}-alkylamino; piperidinylaminoC_{1-6}-alkylaminoC_{1-6}-alkyl; (C_{1-6}-alkylpiperidinyl)(hydroxyC_{1-6}-alkyl)aminoC_{1-6}-alkylamino; (C_{1-6}-alkylpiperidinyl)(hydroxyC_{1-6}-alkyl)aminoC_{1-6}-alkylaminoC_{1-6}-alkyl; hydroxyC_{1-6}-alkyloxyC_{1-6}-alkylpiperazinyl; hydroxyC_{1-6}-alkyloxyC_{1-6}-alkylpiperazinylC_{1-6}-alkyl; (hydroxyC_{1-6}-alkyl)(C_{1-6}-alkyl)amino; (hydroxyC_{1-6}-alkyl)(C_{1-6}-alkyl)aminoC_{1-6}-alkyl; hydroxyC_{1-6}-alkylaminoC_{1-6}-alkyl; di(hydroxyC_{1-6}-alkyl)aminoC_{1-6}-alkyl; pyrrolidinylC_{1-6}-alkyl; pyrrolidinylC_{1-6}-alkyloxy; pyrazolyl; thiopyrazolyl; pyrazolyl substituted with two substituents selected from C_{1-6}-alkyl and trihaloC_{1-6}-alkyl; pyridinyl; pyridinyl substituted with C_{1-6}-alkyloxy, aryloxy or aryl; pyrimidinyl; tetrahydropyrimidinylpiperazinyl; tetrahydropyrimidinylpiperazinylC_{1-6}-alkyl; quinolinyl; indolyl; phenyl; phenyl substituted with one, two or three substituents independently selected from halo, amino, nitro,C_{1-6}-alkyl, C_{1-6}-alkyloxy, hydroxyC_{1-4}-alkyl, trifluoromethyl, trifluoromethyloxy, hydroxyC_{1-4}-alkyloxy, C_{1-4}-alkylsulfonyl, C_{1-4}-alkyloxyC_{1-4}-alkyloxy, C_{1-4}-alkyloxycarbonyl,aminoC_{1-4}-alkyloxy, di(C_{1-4}-alkyl)aminoC_{1-4}-alkyloxy, di(C_{1-4}-alkyl)amino, di(C_{1-4}-alkyl)aminocarbonyl, di(C_{1-4}-alkyl)aminoC_{1-4}-alkyl, di(C_{1-4}-alkyl)aminoC_{1-4}-alkylaminoC_{1-4}-alkyl, di(C_{1-4}-alkyl)amino(C_{1-4}-alkyl)amino, di(C_{1-4}-alkyl)amino(C_{1-4}-alkyl)aminoC_{1-4}-alkyl, di(C_{1-4}-alkyl)aminoC_{1-4}-alkyl(C_{1-4}-alkyl)amino, di(C_{1-4}-alkyl)aminoC_{1-4}-alkyl(C_{1-4}-alkyl)aminoC_{1-4}-alkyl, aminosulfonylamino(C_{1-4}-alkyl)amino, aminosulfonylamino(C_{1-4}-alkyl)aminoC_{1-4}-alkyl, di(C_{1-4}-alkyl)aminosulfonylamino(C_{1-4}-alkyl)amino, di(C_{1-4}-alkyl)aminosulfonylamino(C_{1-4}-alkyl)aminoC_{1-4}-alkyl, cyano, piperidinylC_{1-4}-alkyloxy, pyrrolidinylC_{1-4}-alkyloxy, aminosulfonylpiperazinyl, aminosulfonylpiperazinylC_{1-4}-alkyl, di(C_{1-4}-

alkyl)aminosulfonylpiperazinyl, di(C_{1-4}-alkyl)aminosulfonylpiperazinylC_{1-4}-alkyl, hydroxyC_{1-4}-alkylpiperazinyl, hydroxyC_{1-4}-alkylpiperazinylC_{1-4}-alkyl, C_{1-4}-alkyloxypiperidinyl, C_{1-4}-alkyloxypiperdinylC_{1-4}-alkyl, hydroxyC_{1-4}-alkyloxyC_{1-4}-alkylpiperazinyl,hydroxyC_{1-4}-alkyloxyC_{1-4}-alkylpiperazinylC_{1-4}-alkyl, (hydroxyC_{1-4}-alkyl)(C_{1-4}-alkyl)amino, (hydroxyC_{1-4}-alkyl)(C_{1-4}-alkyl)aminoC_{1-4}-alkyl, di(hydroxyC_{1-4}-alkyl)amino, di(hydroxyC_{1-4}-alkyl)aminoC_{1-4}-alkyl, furanyl, furanyl substituted with-CH=CH-CH=CH-, pyrrolidinylC_{1-4}-alkyl, pyrrolidinylC_{1-4}-alkyloxy, morpholinyl, morpholinylC_{1-4}-alkyloxy, morpholinylC_{1-4}-alkyl,morpholinylC_{1-4}-alkylamino, morpholinylC_{1-4}-alkylaminoC_{1-4}-alkyl, piperazinyl, C_{1-4}-alkylpiperazinyl, C_{1-4}-alkylpiperazinylC_{1-4}-alkyloxy, piperazinylC_{1-4}-alkyl, C_{1-4}-alkylpiperazinylC_{1-4}-alkyl, C_{1-4}-alkylpiperazinylC_{1-4}-alkylamino, C_{1-4}-alkylpiperazinylC_{1-4}-alkylaminoC_{1-6}-alkyl, tetrahydropyrimidinylpiperazinyl, tetrahydropyrimidinylpiperazinylC_{1-4}-alkyl, piperidinylaminoC_{1-4}-alkylamino, piperidinylaminoC_{1-4}-alkylaminoC_{1-4}-alkyl, (C_{1-4}-alkylpiperidinyl)(hydroxyC_{1-4}-alkyl)aminoC_{1-4}-alkylamino, (C_{1-4}-alkylpiperidinyl)(hydroxyC_{1-4}-alkyl)aminoC_{1-4}-alkylaminoC_{1-4}-alkyl, pyridinylC_{1-4}-alkyloxy, hydroxyC_{1-4}-alkylamino, hydroxyC_{1-4}-alkylaminoC_{1-4}-alkyl, di(C_{1-4}-alkyl)aminoC_{1-4}-alkylamino, aminothiadiazolyl,aminosulfonylpiperazinylC_{1-4}-alkyloxy, and thiophenylC_{1-4}-alkylamino;

the central moiety

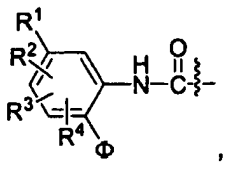


is optionally bridged (*i.e.*, forming a bicyclic moiety) with a methylene, ethylene or propylene bridge;

each R^5 and R^6 can be placed on the nitrogen in replacement of the hydrogen;

aryl in the above is phenyl, or phenyl substituted with one or more substituents each independently selected from halo, C_{1-6}-alkyl, C_{1-6}-alkyloxy, trifluoromethyl, cyano, and hydroxycarbonyl.

[0106] In the compounds of paragraph [0105], R^1, R^2, R^3, and R^4 are preferably as defined in paragraphs [0059] and [0060]. In other embodiments of the compounds of paragraph [0105], R^1, R^2, R^3, and R^4 are all H. Other preferred embodiments of the compounds of paragraph [0105] include the compounds of pages 21 and 22 and Table F-1 of WO 03/076422 in which the terminal hydroxamic acid moiety (HO-NH-C(O)-) is replaced with



wherein Φ, R^1, R^2, R^3, and R^4 are as defined in accordance with paragraph [0057], and preferably [0059] and [0060].

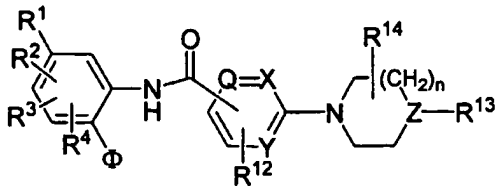
[0107] In paragraph [0105] the definitions in paragraphs [0108] - [0110] supplement the definitions in paragraphs [0031] - [0053]. To the extent there are any inconsistencies between the definitions in paragraphs [0031] - [0053] and in paragraphs [0108] - [0110], the definitions in paragraphs [0108] - [0110] take precedence for the compounds of paragraph [0105] only.

[0108] Halo is generic to fluoro, chloro, bromo and iodo; C_{1-4}-alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, e.g., methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl and the like; C_{1-6}-alky includes C_{1-4}-alkyl and the higher homologues thereof having 5 to 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like; C_{1-6}-alkanediyl defines bivalent straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the branched isomers thereof such as, 2- methylpentanediyl, 3-methylpentanediyl, 2,2-dimethylbutanediyl, 2,3-dimethylbutanediyl and the like; trihaloC_{1-6}-alkyl defines C_{1-6}-alkyl containing three identical or different halo substituents for example trifluoromethyl; C_{2-6}-alkenediyl defines bivalent straight and branched chain hydrocarbon radicals containing one double bond and having from 2 to 6 carbon atoms such as, for example, ethenediyl, 2-propenediyl, 3-butenediyl, 2-pentenediyl, 3-pentenediyl, 3-methyl-2-butenediyl, and the like; aryl defines phenyl, and phenyl substituted with one or more substituents each independently selected from halo, C_{1-6}-alkyl, C_{1-6}-alkyloxy or trifluoromethyl, cyano, hydroxycarbonyl; aminoaryl defines aryl substituted with amino; C_{3-10}-cycloalkyl includes cyclic hydrocarbon groups having from 3 to 10 carbons, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl and the like.

[0109] The term "another Zn-chelating group" refers to a group which is capable of interacting with a Zn^{2+}-ion, which can be present at an enzymatic binding site.

[0110] The N-oxide forms of the compounds of paragraph [0105] comprise those compounds wherein one or several nitrogen atoms are oxidized to the so-called N-oxide, particularly those N-oxides wherein one or more of the piperidine-, piperazine or pyridazinyl-nitrogens are N-oxidized.

[0111] In another embodiment, the invention comprises compounds of the following structural formula (5):



(5)

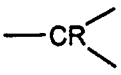
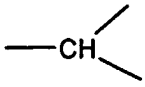
or a pharmaceutically acceptable salt thereof, wherein

Φ is $-NH_2$ or $-OH$;

R^1 is H or as defined in paragraph [0046];

R^2, R^3, and R^4 are as defined in paragraph [0046];

n is 0, 1, 2 or 3 and when n is 0 then a direct bond is intended;

Q is nitrogen or  ,  , or  ;

X is nitrogen or  ;

Y is nitrogen or  ;

Z is nitrogen or  ;

R is selected from the group consisting of hydrogen, halogen, $-NH_2$, nitro, hydroxy, aryl, heterocyclyl, C_3-C_8-cycloalkyl, heteroaryl, C_1-C_7-akyl, haloalkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, C_1-C_7-acyl, C_1-C_7-alkyl-aryloxy, C_1-C_7-alkyl-arylsulfanyl, C_1-C_7-alkyl-arylsulfinyl, C_1-C_7-alkyl-arylsulfonyl, C_1-C_7-alkyl-arylaminosulfonyl, C_1-C_7-alkyl-arylamine, C_1-C_7-alkynyl-C(O)-amine, C_1-C_7-alkenyl-C(O)-amine, C_1-C_7-alkynyl-R^9, C_1-C_7-alkenyl-R^9 wherein R^9 is hydrogen , hydroxy, amino, C_1-C_7-alkyl or C_1-C_7-alkoxy;

R^{12} **is hydrogen, halo, hydroxy, amino, nitro, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, di(C_{1-6}alkyl)amino, hydroxyamino or naphtalenylsulfonylpyrazinyl;**

R^{13} **is hydrogen, C_{1-6}alkyl, arylC_{2-6}alkenediyl, furanylcarbonyl, naphtalenylcarbonyl, -C(O)phenylR^9, C_{1-6}alkylaminocarbonyl, aminosulfonyl, arylaminosulfonyl, aminosulfonylamino, di(C_{1-6}alkyl)aminosulfonylamino, arylaminosulfonylamino, aminosulfonylaminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminosulfonylaminoC_{1-6}alkyl, arylaminosulfonylaminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-12}alkylsulfonyl, di(C_{1-6}alkyl)aminosulfonyl, trihaloC_{1-6}alkylsulfonyl, di(aryl)C_{1-6}alkylcarbonyl, thiophenylC_{1-6}alkylcarbonyl, pyridinylcarbonyl or arylC_{1-6}alkylcarbonyl**

wherein each R^9 is independently selected from phenyl; phenyl substituted with one, two or three substituents independently selected from halo, amino, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkyloxy, aminoC_{1-4}alkyloxy, di(C_{1-4}alkyl)aminoC_{1-4}alkyloxy, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, hydroxyC_{1-4}alkylpiperazinylC_{1-4}alkyl, C_{1-4}alkyloxypiperidinylC_{1-4}alkyl, hydroxyC_{1-4}alkyloxyC_{1-4}alkylpiperazinyl, C_{1-4}alkylpiperazinylC_{1-4}alkyl, di(hydroxyC_{1-4}alkyl)aminoC_{1-4}alkyl, pyrrolidinylC_{1-4}alkyloxy, morpholinylC_{1-4}alkyloxy, or morpholinylC_{1-4}alkyl; thiophenyl; or thiophenyl substituted with di(C_{1-4}alkyl)aminoC_{1-4}alkyloxy, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, pyrrolidinylC_{1-4}alkyloxy, C_{1-4}alkylpiperazinylC_{1-4}alkyl, di(hydroxyC_{1-4}alkyl)aminoC_{1-4}alkyl or morpholinylC_{1-4}alkyloxy.

R^{14} is hydrogen, hydroxy, amino, hydroxyC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl, aminocarbonyl, hydroxycarbonyl, aminoC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, hydroxycarbonylC_{1-6}alkyl, hydroxyaminocarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminoC_{1-6}alkyl or di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

when R^{13} & R^{14} are present on the same carbon atom, R^{13} & R^{14} together may form a bivalent radical of formula

-C(O)-NH-CH_2-NR^{10}- (a-1)

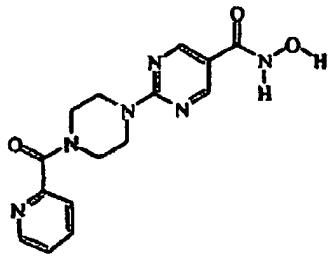
wherein R^{10} is hydrogen or aryl;

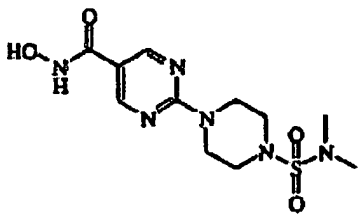
when R^{13} & R^{14} are present on adjacent carbon atoms, R^{13} & R^{14} together may form a bivalent radical of formula

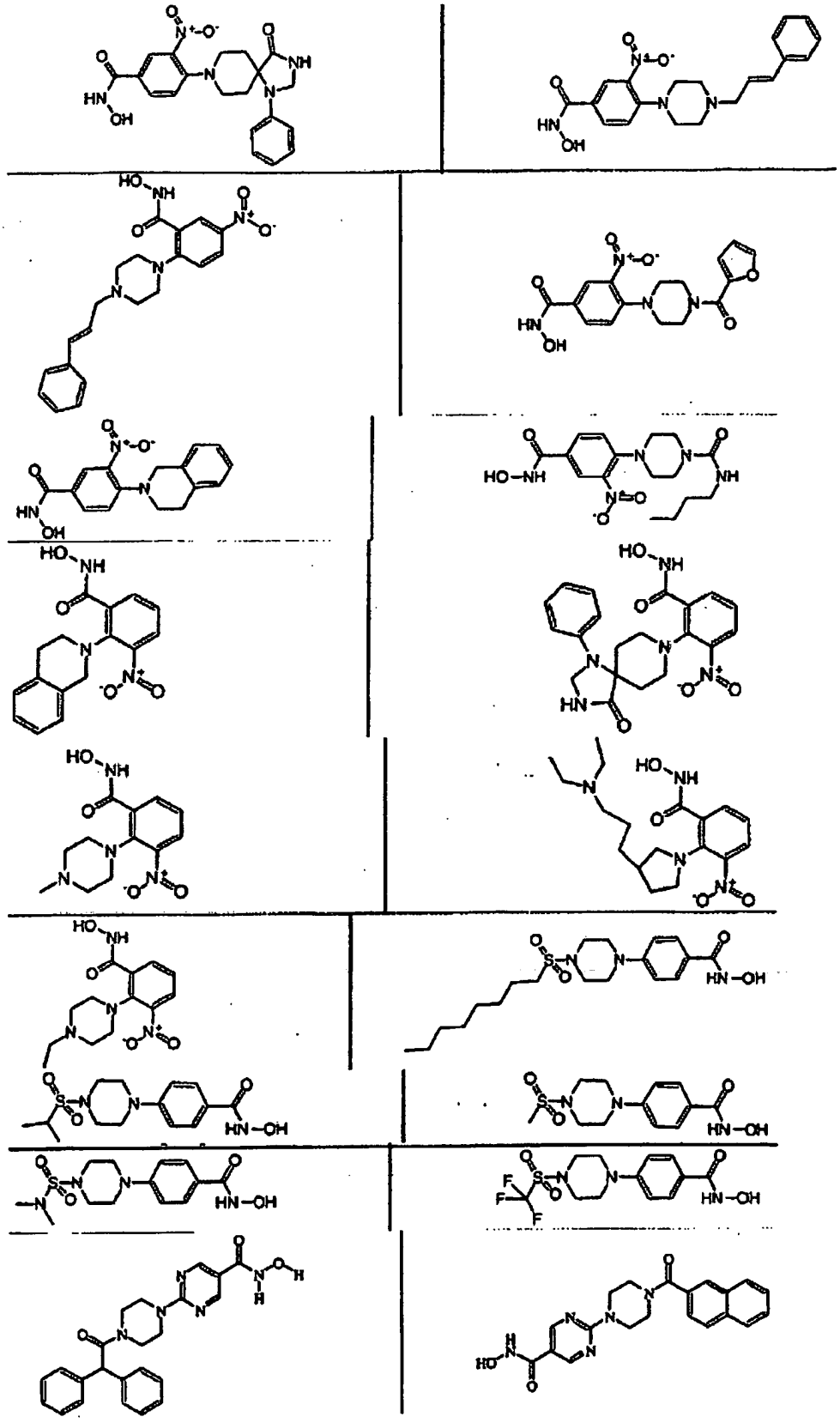
=CH-CH=CH-CH= (b-1);

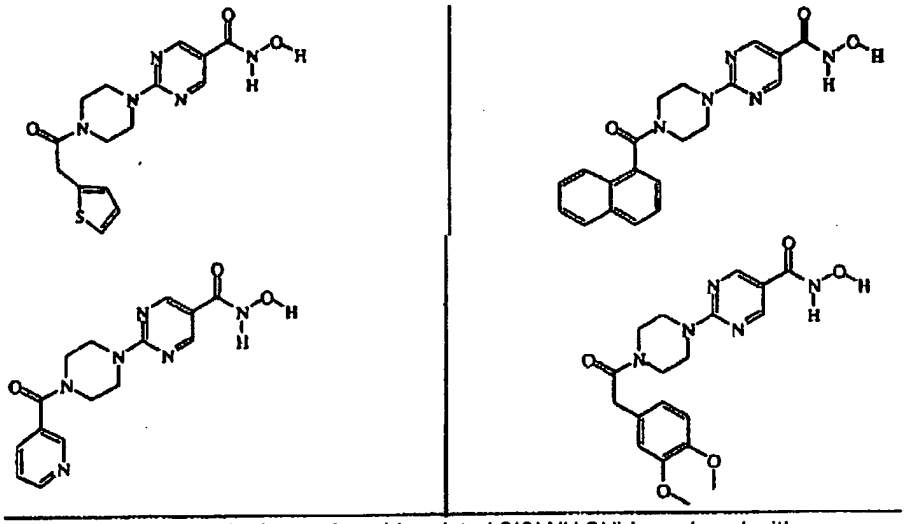
aryl in the above is phenyl, or phenyl substituted with one or more substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, cyano or hydroxycarbonyl.

[0112] Particular embodiments of the compound according to paragraph [0111] include the following

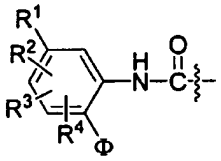








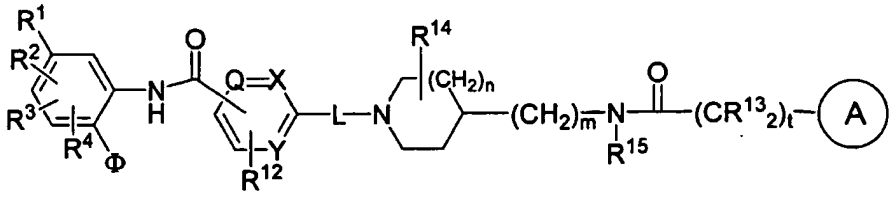
in which the terminal hydroxamic acid moiety (-C(O)-NH-OH) is replaced with



wherein Φ, R^1, R^2, R^3, and R^4 are as defined in accordance with paragraph [0057], and preferably [0059] and [0060].

[0113] In the compounds of paragraphs [0111]-[0112], R^1, R^2, R^3, and R^4 are preferably as defined in paragraphs [0059] and [0060], while in other embodiments of the compounds of paragraphs [0111]-[0112], R^1, R^2, R^3, and R^4 are all H.

[0114] In another embodiment, the invention comprises compounds of the following structural formula (6):



(6)

or a pharmaceutically acceptable salt thereof, wherein

Φ is $-NH_2$ or $-OH$;

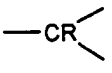
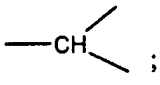
R^1 is H or as defined in paragraph [0046];

R^2, R^3, and R^4 are as defined in paragraph [0046];

n is 0, 1, 2 or 3 and when n is 0 then a direct bond is intended;

m is 0 or 1 and when m is 0 then a direct bond is intended;

t is 0, 1, 2, 3 or 4 and when t is 0 then a direct bond is intended;

Q is nitrogen or  ,  , or  ;

X is nitrogen or  ;

Y is nitrogen or  ;

R is selected from the group consisting of hydrogen, halogen, $-NH_2$, nitro, hydroxy, aryl, heterocyclyl, C_3-C_8-cycloalkyl, heteroaryl, C_1-C_7-akyl, haloalkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, C_1-C_7-acyl, C_1-C_7-alkyl-aryloxy, C_1-C_7-alkyl-arylsulfanyl, C_1-C_7-alkyl-arylsulfinyl, C_1-C_7-alkyl-arylsulfonyl, C_1-C_7-alkyl-arylaminosulfonyl, C_1-C_7-alkyl-arylamine, C_1-C_7-alkynyl-C(O)-amine, C_1-C_7-alkenyl-C(O)-amine, C_1-C_7-alkynyl-R^9, C_1-C_7-alkenyl-R^9 wherein R^9 is hydrogen , hydroxy, amino, C_1-C_7-alkyl or C_1-C_7-alkoxy;

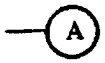
R^{12} is hydrogen, halo, hydroxy, amino, nitro, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, di(C_{1-6}alkyl)amino, hydroxyamino or naphtalenylsulfonylpyrazinyl;

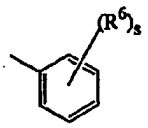
-L- is a direct bond or a bivalent radical selected from C_{1-6}alkanediyl, C_{1-6}alkanediyloxy, amino, carbonyl or aminocarbonyl;

each R^{13} is independently represents a hydrogen atom and one hydrogen atom can be replaced by a substituent selected from aryl;

R^{14} is hydrogen, hydroxy, amino, hydroxyC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl, aminocarbonyl, hydroxycarbonyl, aminoC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, hydroxycarbonylC_{1-6}alkyl, hydroxyaminocarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminoC_{1-6}alkyl or di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl or aryl;

 is a radical selected from



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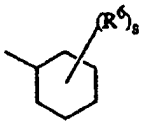

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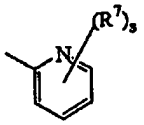

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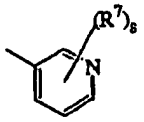

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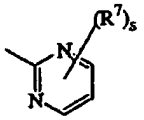

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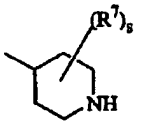

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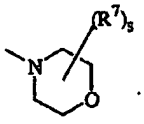

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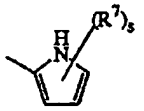

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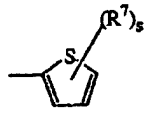

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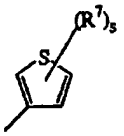

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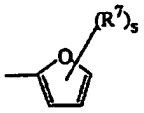

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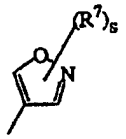

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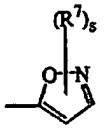

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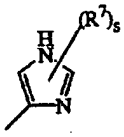

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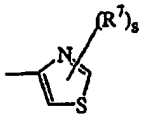

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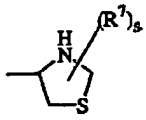

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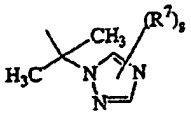

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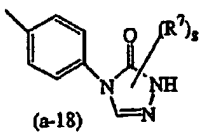

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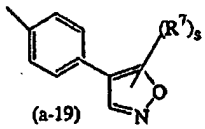

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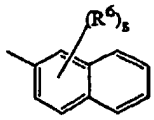

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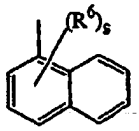

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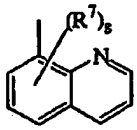

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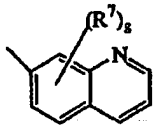

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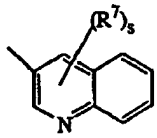

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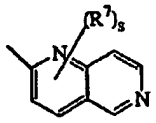

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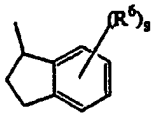

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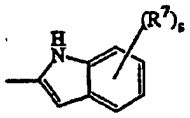

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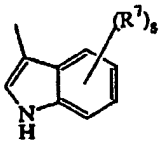

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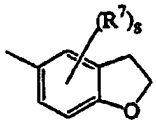

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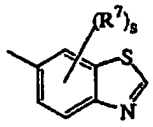

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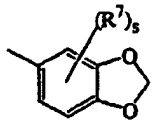

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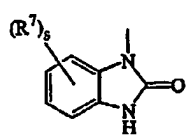

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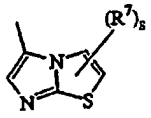

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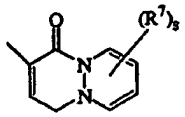

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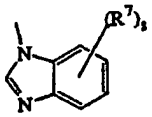

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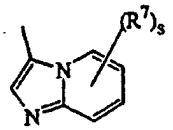

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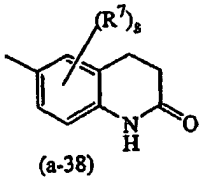

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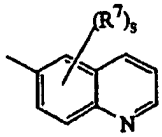

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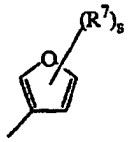

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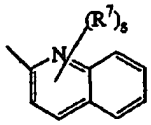

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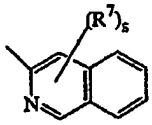

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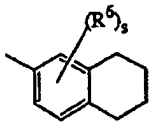

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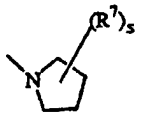

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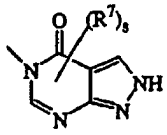

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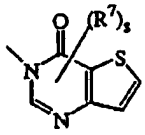

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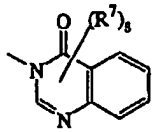

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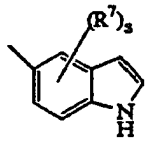

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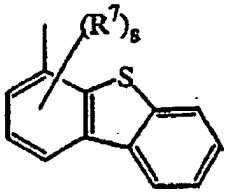

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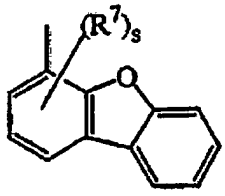

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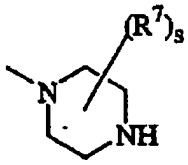

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